

Linköping University Medical Dissertations
No. 867

Acupuncture

**the effects on muscle blood flow
and aspects of treatment in the clinical context**



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Linköping 2004

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ISBN 91-7373-841-7

ISSN 0345-0082

Printed in Sweden by Unityck, Linköping 2004

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ABSTRACT

The overall aim of this thesis was to elucidate and investigate psychophysiological aspects and effects of acupuncture and needle stimulation. Within this framework emphasis was directed toward the effects of needle stimulation (acupuncture) on muscle blood flow in the tibialis anterior and trapezius muscles in healthy subjects and patients suffering from chronic muscle pain. This study also included evaluation of a new application of photoplethysmography in non-invasive monitoring of muscle blood flow. The evaluation was based on experiments known to provoke skin or muscle blood flow. The psychological aspects studied comprised the effects of manual acupuncture on pain in fibromyalgia patients and the effects of electro-acupuncture on psychological distress and vasomotor symptoms in postmenopausal women in the clinical context.

The results showed that photoplethysmography have potential to non-invasively monitor muscle blood flow and to discriminate between blood flow in skin and muscle, although some considerations still have to be accounted for. It was further shown that muscle blood flow change in response to needle stimulation differed between healthy subjects and patients. Deep needle stimulation in the muscle of healthy subjects consistently increased muscle blood flow more than subcutaneous needle stimulation. In the painful trapezius muscle of FMS patients, however, subcutaneous needling was equal or even more effective in increasing muscle blood flow than deep intramuscular stimulation. Generally, needle stimuli had weak effect on blood flow in the trapezius muscle of the severely affected trapezius myalgia patients, possibly depending on older age and lesser number of patients included in the study. The different patterns of blood flow response to needle stimulation between healthy subjects and patients with chronic muscle pain might be a manifestation of altered somatosensory processing in the patients.

The clinical studies showed that best pain relief of acupuncture in FMS patients was achieved in the neck-shoulder region, while the effect on the generalised symptoms was of short duration. Well-being and sleep was found to best predict treatment outcome. The results suggest that acupuncture treatment may be used for the alleviation of neck-shoulder pain, primarily, but it is not an alternative as the sole treatment. Electro-acupuncture, significantly decreased psychological distress and climacteric symptoms in postmenopausal women, but not better than a (near-) placebo control, implying pronounced non-specific effects.

ABBREVIATIONS

AA	Acupuncture analgesia
AROM	Active range of movement
AVA	Arteriovenous anastomose
CGRP	Calcitonin gene-related peptide
CCK	Cholecystokinin
CT	Highly sensitive tactile C-fibres
Deep	Deep needling involving the “DeQi” sensation
DeQi	A characteristic sensation of numbness, aching, distension, heaviness or soreness raised when rotating an acupuncture needle forward-backwards 180°.
EA	Electro-acupuncture
FBF	Mean femoral blood flow
fMRJ	Functional magnetic resonance imaging
FMS	Fibromyalgia syndrome
GCSI	General climacteric symptom intensity
HS	Healthy subjects
IR	Infra-red light
LDF	Laser Doppler flowmetry
LED	Light emitting diode
NA	Noradrenaline
NO	Nitric oxide
NPY	Neuropeptide Y
PD	Photo detector
PET	Positron emission tomography
POM	Power Optical Meter
PPG	Photoplethysmography
PPT	Pressure pain threshold
SC	Subcutaneous needle stimulation
SNI	Superficial needle insertion
SP	Substance P
TM	Trapezius myalgia
TP	Tender point
VAS	Visual analogue scale

LIST OF PAPERS

This thesis is based on the following studies, which will be referred to in the text by their Roman numerals, I-VI.

- I. Sandberg M, Lundeberg T, Gerdle B. Manual acupuncture in fibromyalgia: a long-term pilot study. *J Musculoskel Pain* 1999; 7(3): 39-58.
- II. Sandberg M, Wijma K, Wyon Y, Nedstrand E, Hammar M. Effects of electro-acupuncture on psychological distress in postmenopausal women. *J Complem Ther Med* 2002; 10: 161-169.
- III. Sandberg, M, Zhang Q, Styf J, Gerdle B, Lindberg L-G. Non-invasive monitoring of muscle perfusion utilising photoplethysmography - evaluation of a new application. Submitted to *Acta Physiol Scand* (in revision).
- IV. Sandberg M, Lundeberg T, Lindberg L-G, Gerdle B. Effects of acupuncture on skin and muscle blood flow in healthy subjects. *Eur J Appl Physiol* 2003; 90: 114-119.
- V. Sandberg M, Lindberg L-G, Gerdle B. Peripheral effects of needle stimulation (acupuncture) on skin and muscle blood flow in fibromyalgia. *Eur J Pain* 2004; 8: 163-171.
- VI. Sandberg M, Larsson B, Lindberg L-G, Gerdle B. Different patterns of blood flow response in the trapezius muscle following needle stimulation (acupuncture) between healthy subjects and patients with fibromyalgia and work-related trapezius myalgia. Accepted in *Eur J Pain*.

Note that in Study III, the term *blood flow* is replaced with the term *blood perfusion*.

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INTRODUCTION

In 1984 acupuncture was accepted into General Practice in Sweden for the treatment of pain. In general, common knowledge of biological mechanisms behind the effects of acupuncture was very limited and scepticism prevailed in the medical care at that time. In 1986 I started to treat patients with acupuncture, mostly patients suffering from rheumatoid arthritis (RA) but also some patients with fibromyalgia (FMS). The pain alleviating response in RA patients was generally positive, whereas the effect on FMS patients was more ambiguous. However, since acupuncture generally seemed to reduce pain more than any other physical treatment modality these patients had tried previously, it was a challenge to explore this field further and I started to document response to the treatment in more detail. Furthermore, during the first years of practicing acupuncture, I gradually became increasingly aware of the importance of my own behaviour and care of the patients.

The major aim of the experimental research was to explore the effects of acupuncture on blood flow in painful muscles in patients suffering from chronic neck-shoulder pain. These studies were based on early clinical observations of acupuncture improving pain and range of movement in the neck-and shoulder area in some patients, also in certain FMS patients. They were also based on patients' reports of previous experiences of acupuncture when visiting practitioners of alternative medicine.

Close cooperation with the Department of Biomedical Engineering of the University of Linköping was a prerequisite for the experimental blood flow studies. As a result the study included clinical evaluation of photoplethysmography (PPG) in non-invasive monitoring of muscle blood flow. Since the PPG technique was under development and previous studies had been performed on the tibialis muscle, it was decided to start at this site. In two studies blood flow was monitored simultaneously on the contralateral side with another probe. In order to obtain an idea of the extent of the blood flow increase, the subjects in study VI indicated their sensation of warmth evoked by the needling by using body charts.

BACKGROUND

Pain

One of the vital functions of the nervous system is to provide information about the occurrence or threat of injury and the sensation of pain contributes to this function. Response to noxious stimuli, nociception, provides a signal to alert the organism of potential injury. Physiological pain is initiated by excitation of nociceptor fibres innervating peripheral tissues and activated only by noxious stimuli. The sensory inflow generated by nociceptors activates neurones in the spinal cord, which project to the cortex via a relay in the thalamus, eliciting pain. The nociceptive input also activates reflex withdrawal, an increase in arousal and emotional, autonomic and neurohumoral responses, reflecting the complex nature of pain (Woolf and Salter 2000).

Nociception is not equal to pain, which comprises a complex course of processes within the nervous system until the individual perception and experience is formed. The International Association for the Study of Pain (IASP) clearly states this point by defining pain as *an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage* (Merskey 1979).

Nociception might indirectly be modulated by emotional factors and mental stress, and pain *per se* can also act as an important stressor (Roatta, Kalezic et al. 2003). Modulations of peripheral and central processing of noxious input, such as hypersensitivity, are normal events in response to tissue damage or inflammation and usually return to normal if the disease process is controlled (Woolf and Salter 2000). Chronic pain persists beyond the expected course of an acute disease, or beyond a defined time point (i.e. 3 or 6 months) and is a complex perception that has profound affective and cognitive features. During chronic pain the autonomic nervous system may undergo plastic changes (Roatta, Kalezic et al. 2003). A major cause of chronic pain is suggested to be the expression of long-lasting neural plasticity of the pain transmission system, also involving psychological factors, and which eventually may lead to irreversible structural changes in central pain pathways (Sandkuhler 1996; Woolf and Salter 2000; Mense 2003; Windhorst 2003). Recent studies of the human brain using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) reveal activation of extended cortical regions in response to noxious stimuli in chronic pain conditions (Gracely, Petzke et al. 2002; Giesecke, Gracely et al. 2004).

Muscle pain

Muscle pain differs in several respects from cutaneous pain. While cutaneous pain is characterised by its sharp, pricking, or burning nature, muscle pain is

perceived as dull, aching and cramp-like (Mense 2003). Muscle pain is difficult to localise and often shows patterns of referral to other deep somatic structures, in contrast to cutaneous pain. The information from muscle nociceptors is processed differently in the central nervous system (Svensson, Minoshima et al. 1997; Sluka 2002) and inhibited more strongly by the descending pain control pathways compared to cutaneous pain (Mense 2003).

Nociceptors are found in connective tissue and along the wall of arterioles but not in muscle fibres themselves (Mense 1993). Nociceptors in skeletal muscle are free nerve endings connected to the CNS by high-threshold thin myelinated (group III) or unmyelinated (group IV) nerve fibres (Mense 2003). A high proportion of group III afferents are attached to low-threshold mechanoreceptors (ergoreceptors) and strongly activated during forceful stretching and exercise (Mense and Meyer 1985). Ergoreceptors are suggested to play a role in the cardiovascular and respiratory adjustments occurring during exercise (Kniffeki, Mense et al. 1981), and there is some evidence indicating that ergoreceptors may form the afferent limb for exercise- and acupuncture-induced hypoalgesia (Mense 2003). Sensory nerve fibres in muscle present a similar peptide pattern to that of cutaneous nerves, i.e. they contain neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) (Mense 2003).

Most nociceptors have high stimulation threshold and do not respond to everyday stimuli but can be sensitised by endogenous pain-producing substances such as bradykinin, 5-hydroxytryptamine and high concentrations of potassium ions. Long-lasting pathologic alterations in muscle tissue, such as during ischaemia or inflammation, sensitise muscle nociceptors and increase the innervation density of muscle tissue with neuropeptide-containing nerve endings. Input from muscle nociceptors to the spinal cord or brain are particularly effective in inducing neuroplastic changes (Mense 2003).

Mental stress may be of crucial importance for muscle nociception and pain by increasing sympathetic nerve activity, especially during chronic stress. Under conditions of increased sympathetic activity, such as stress or exercise, the performance of fast-contracting muscles may be improved, whereas opposite actions are exerted by catecholamines on slow-contracting muscles (Passatore and Roatta 2003)

Central sensitisation opens silent synapses leading to an increased proportion of neurones responding to weak mechanical stimuli, and to enlarged receptive fields. The target area of the muscle in the spinal cord, or brain stem, may expand. Referral of muscle pain, which is common in patients with muscle pain, can be explained by this phenomenon. These changes are considered as important steps in the transition from acute to chronic pain (Woolf and Salter 2000; Mense 2003). Another step toward chronic pain is the development of metabolic changes in sensory spinal neurones (Mense 2003).

It is suggested that enhanced pain sensation, i.e. hyperalgesia, at least partly results from increased central hyperexcitability and spontaneous pain from increased background activity of dorsal horn neurones (Mense 2003). Primary hyperalgesia refers to increased pain sensation within the area of injured or inflamed tissue and is best explained by changes in the properties of primary nociceptive afferents (Koltzenburg 2000). Secondary hyperalgesia appears outside this area and critically requires functional changes in the central nervous system. Structural changes in the circuitry of the spinal dorsal horn, such as sprouting of the spinal terminals of afferent fibres and new formation and broadening of synaptic contacts, may lead to the initial functional changes becoming permanent and the function of the spinal cord altered persistently (Sandkuhler 1996; Woolf and Salter 2000; Mense 2003).

Peripheral microcirculation

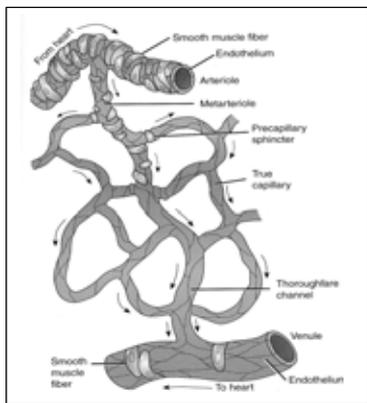


Figure 1: Arteriole, capillaires and venule (from Tortora Grabowski; Principles of Anatomy and Physiology, HarperCollins College Publisher 1996).

with precapillary sphincters. Throughfare channels bypass the capillary bed when the precapillary sphincters are constricted. The walls of arterioles, metarterioles and precapillary sphincters contain smooth muscle layers, which are richly innervated. Capillaries are thin structures with tubular walls of single-layer, highly permeable endothelial cells.

The peripheral circulation is essentially under dual control: extrinsic control by the nervous system and intrinsic control by the conditions in the tissues surrounding the blood vessels (Tortora and Grabowski 2000). Extrinsic control includes neural regulation by vasoconstrictor fibres of the sympathetic nervous system, humoral factors and sensory dilator axons. Intrinsic control includes mechanisms such as autoregulation, endothelium-mediated regulation, metabolic regulations, and ascending dilatation.

Arterioles regulate the rate of blood flow to various tissues, by allowing passage of blood from arteries to capillaries where the interchange of nutrients and cellular excreta between the tissues and circulating blood occurs (**Figure 1**) (Tortora and Grabowski 2000).

Before entering the capillaries blood from arterioles passes into a series of metarterioles

Efferent function of dorsal root ganglion nerves

Blood vessels in skin and other tissues are supplied by sensory nerve fibres, which contain neuropeptides such as SP and CGRP (Franco-Cereceda, Henke et al. 1987). Human skin contains several types of C nociceptors with distinctly different properties (Torebjörk 1999). Apart from signaling pain, nociceptors also regulate vascular function by antidromic release of neuropeptides from peripheral nerve terminals upon activation, directly and via axon reflex mechanisms (Holzer 1988; Koltzenburg, Lewin et al. 1990; Maggi 1991; Holzer 1992) (**Figure 2**).

CGRP is a neuropeptide with highly potent vasodilator properties and is primarily synthesised in the dorsal root ganglia neurones and transported in unmyelinated C- and small myelinated A δ -axons to the nerve endings (Brain, Williams et al. 1985). This vasodilatation, which becomes visible as a flare at the site of the stimulus is an efferent event that depends on activity in afferent nociceptive fibres, and is part of neurogenic inflammation (Holzer 1988; Jänig and Lisney 1989; Kashiba and Ueda 1991; Holzer 1992; Kolston and Lisney 1993; Brain and Cambridge 1996; Brain 1997) and is independent of the autonomic nervous system (Blumberg and Wallin 1987).

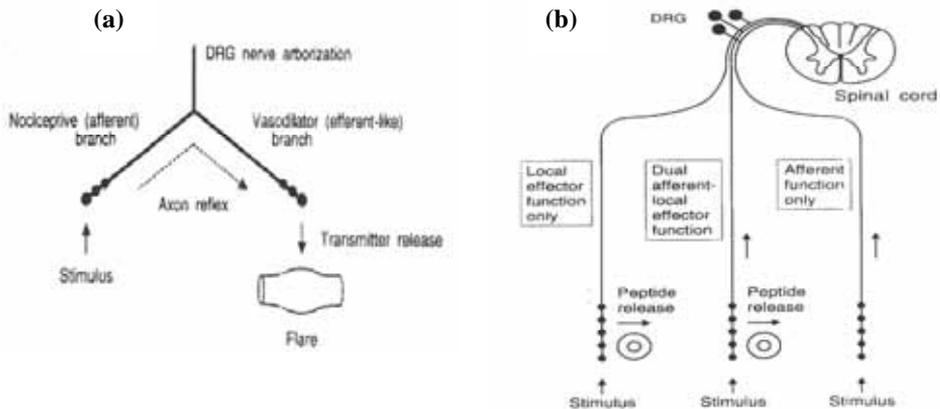


Figure 2 : Flare spreading via an axon reflex (a). Heterogeneity of DRG neurones with a purely local effector function (a), a mixed afferent-local effector function (b), and a purely afferent function (c). DRG=dorsal root ganglion neuron (Reprinted from. *Neuroscience*, Vol 86, Holzer and Maggi, *Dissociation of dorsal root ganglion neurons into afferent and efferent-like neurons*, pp. 389-398, 1998, with permission from Elsevier).

By antidromic activation of collaterals in adjacent tissue, and by dorsal root reflexes, the nociceptive stimulus results in vasodilatation and increased blood flow extending the site of stimulus by far (Holzer 1988; Holzer 1992; Willis 1999; Schmelz, Michael et al. 2000), and may also spread beyond midline of the body (LaMotte, Shain et al. 1991; Rees, Sluka et al. 1996). Furthermore, by the presence of dichotomising spinal nerves, which branch to different types of

tissue, axon reflexes may also induce vasodilatation and increased blood flow in remote tissues (Dawson et al., 1992; Hotta et al, 1996).

Antidromic vasodilatation has a tardy development, with a latency of ~15-20 s, and outlasts the time of stimulation (Holzer 1992; Häbler, Wasner et al. 1997). This time course was also described in vasodilatation induced by intradermally applied CGRP (Weidner, Klede et al. 2000), but is in contrast to sympathetically induced vasoconstriction which is rapid and lasts only a few seconds after cessation of the noradrenaline (NA) secretion (Häbler, Wasner et al. 1997). However, during strong sympathetic reflex activation the co-release of neuropeptide Y (NPY) from the sympathetic nerve terminals induces long-term vasoconstriction in both skin and muscle (Lundberg, Pernow et al. 1987)

Sympathetic regulation

The pathways controlling the sympathetic vasoconstrictor fibres originate in the medulla of the brainstem and are under control of sensory receptors and higher brain regions, including the cerebral cortex, limbic system, hypothalamus, and skin (Tortora and Grabowski 2000). Structures in the hypothalamus are responsible for behavioural and emotional control of the cardiovascular system and the temperature-regulating centre affects the blood vessels in the skin in order to restore body temperature. The opiate system seems to play a role in cardiovascular functioning and thermoregulation, especially in response to stress (Olson, Olson et al. 1991). Cerebrospinal vasoconstrictors are tonically active, causing a basal vessel tone. Inhibition of the vasoconstrictor areas results in vasodilatation, while activation leads to increased sympathetic tone. The sympathetic vasoconstrictor activity in the skin is regulated independently of that in muscle. As a result, sympathetic nerve activity in the skin can be increased at the same time as sympathetic nerve activity in muscle is decreased (Tortora and Grabowski 2000).

Skin structure and microcirculation

The thickness of the skin is 1-4 mm, depending on location, but over most part of the body it is 1-2 mm. Structurally, the skin consists of two principle parts, epidermis and dermis (Tortora and Grabowski 2000) (**Figure 3**). The superficial epidermis is composed of epithelial tissue, with the upper layers consisting of dead keratinocytes. The dermis is a thicker layer and composed mainly of connective tissue, where blood vessels, nerves, glands, and hair follicles are embedded. Its surface area is greatly increased by dermal papillae, containing loops of capillaries emerging from the superficial plexus at the papillary dermal boundary. Whereas the epidermis is avascular, the dermis is well vascularised and regulated almost totally by sympathetic nerves (Tortora and Grabowski 2000).

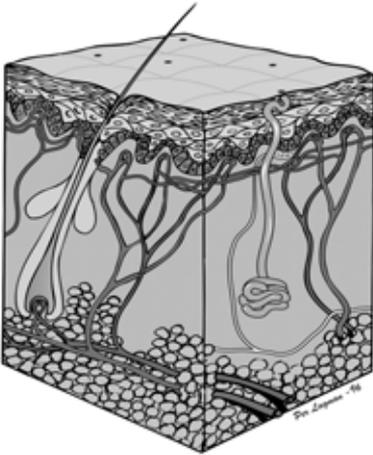


Figure 3: Structure of the skin and underlying tissue.

(Illustration Per Lagman)

the dilatation in response to passive rises in core temperature by 0.5-1.0 °C results in small increases in skin blood flow due to withdrawal of vasoconstrictor tone. During further increase in core temperature there is a marked and progressive rise in skin blood flow that is mediated by increased activity in sympathetic vasodilator (cholinergic) fibres, and is closely associated with sweating (Joyner and Halliwill 2000). The skin itself has a widely varying temperature.

The thermoregulatory state of a subject is suggested to profoundly influence the extent and direction of various cutaneous vasomotor reflex responses (Oberle, Elam et al. 1988). During moderate exercise, skin blood flow may increase, which helps dissipate heat from the body, whereas during strenuous exercise skin blood vessels constrict somewhat, allowing more blood to circulate through contracting muscles (Tortora and Grabowski 2000).

The skin is richly innervated with both myelinated and unmyelinated nerve fibres. Some dermal papillae contain tactile receptors, Meissner corpuscles, sensitive to touch, and free nerve endings. Some of the epidermal axons, emerging from the superficial dermal nerve plexus, contain neuropeptides which are secreted at the epidermal penetration site of the nerves upon activation (Gibbins, Wattchow et al. 1987). The deeper reticular layer of dermis and the subcutaneous layer contain many blood vessels, nerves and free nerve endings. Pacinian corpuscles, sensitive to deep pressure, are distributed throughout the dermis and subcutis (Tortora and Grabowski 2000).

Skeletal muscle structure and microcirculation

Based on structural and functional characteristics, skeletal muscle fibres are classified into different types. Slow oxidative (Type I) fibres contain large amounts of myoglobin, many mitochondria and capillaries. These fibres are very

resistant to fatigue and are found in large numbers in postural muscles. Fast glycolytic (type IIB) fibres have low myoglobin content and relatively few mitochondria and capillaries and fatigue easily. Fast oxidative (Type IIA) fibres are somewhat less resistant to fatigue (Tortora and Grabowski 2000). Human muscles vary with regard to fibre type composition in that each muscle is special and has a unique molecular composition. Differences in the composition of muscle fibres are likely to be of importance in individuals performing low-force repetitive and / or monotonous tasks (Thornell, Kadi et al. 2003). A predominance of Type I fibres in the trapezius muscle (66 %) was reported in cleaners, both with and without myalgia, and suggested to probably reflect the stabilising (postural) demands of the muscle on the scapula when the arm is moving (Larsson, Bjork et al. 2001). Also in the tibialis anterior muscle the fibres are predominantly Type I, slow oxidatative fibres (Blaisdell 2002).

The trapezius muscle is relatively flat and thin and serves an important function in the shoulder girdle, especially as a stabiliser of the scapulae. The trapezius muscle receives its motor supply via the spinal part of the accessory nerve (XI) and branches of the ventral rami of the cervical nerves (C3-4). The skin over the trapezius muscle is supplied by the dorsal rami of C3 - T12, the upper and middle part of the muscle being supplied by the supraclavicular nerve (C3-6). The tibialis anterior muscle receives its motor supply via the deep peroneal nerve (L4-5) and the skin above the muscle is innervated by the lateral sural cutaneous and superficial peroneal nerves (L5, S1-2) (Netter 1991).

Vascular nutrient and hormone delivery to skeletal muscle plays a major role in the regulation of metabolism in skeletal muscle (Clark, Newman et al. 1998). Skeletal muscles are well supplied with nerves and blood vessels, and have high capillary density, especially postural muscles. Arterioles, metarterioles and capillaries are located close to the muscle fibres. Each muscle fibre is in close contact with one or more capillaries (Tortora and Grabowski 2000). The composition of the capillary bed varies between muscles and is closely related to individual fibres. The transverse cervical artery of the subclavian system supplies the trapezius muscle and the blood supply to the tibialis anterior muscle originates from the anterior tibial artery (Netter 1991).

In skeletal muscle, extrinsic and intrinsic mechanisms of microcirculation interact. In resting muscle, neural sympathetic vasoconstrictor tone is dominant and part of the capillary bed of inactive skeletal muscle is temporarily excluded from being perfused (Segal 1999). Various metabolic factors cause the functional hyperaemia associated with exercise (Segal 1999). In addition, CGRP released from sensory nerve endings in the exercising muscle is suggested to contribute to the active hyperaemia (Yamada, Ishikawa et al. 1997; Sato, Sato et al. 2000). During static exercise, the metabolic hyperaemia is less pronounced than during dynamic exercise because the sustained rise in intra-muscular pressure limits the dilatation of arterioles. Blood flow to exercising muscle is simultaneously under both metabolic vasodilator and sympathetic

vasoconstrictor control. NPY is co-released with NA from sympathetic nerves and the adrenal medulla during stress and exercise, causing vasoconstriction. However, in working muscles blood flow is guaranteed since the sympathetically induced muscle vasoconstriction is normally antagonised and overridden by the local vasodilator actions mediated by nitric oxide (NO), and transmitter agents (Passatore and Roatta 2003).

Acute mental stress was shown to increase limb blood flow in healthy individuals through elevation of perfusion pressure and via vasodilatation, suggested to be due to reduction in vasoconstrictor nerve activity, locally mediated NO release and vascular β_2 -adrenoceptor stimulation by circulating adrenaline (Linde, Hjemdahl et al. 1989). However, the response to acute mental stress on muscle blood flow is highly variable among individuals (Joyner and Halliwill 2000). Long-term stress with high levels of cortisol impedes the function of NO in vasodilatation and might lead to a lasting change in the balance between the sympathetic and parasympathetic branches of the autonomic nervous system. This state will affect the regulation of both cortisol and catecholamines, with possible long-term deleterious effects on muscle tissue (Ljung and Friberg 2004). Impaired regulation of microcirculation, regardless of its origin, may be a casual factor in muscle pain (Passatore and Roatta 2003).

Acupuncture

Acupuncture is part of Traditional Chinese Medicine (TCM) and used for treating symptoms and disease. Traditional acupuncture is based on the historical Chinese philosophical ideas of diagnosis and treatment and built on the principle of restoring energy balance. This form of acupuncture is still used in Chinese clinical practice, and also to some extent in Western countries. The characteristic needle sensation, called *DeQi*, achieved by manually lifting and thrusting, or twirling the needle after insertion into tissue, is supposed to be a prerequisite for acupuncture to be effective (Cheng 1987). In China, vigorous needling methods have been described in traditional terms such as “mounting-burning fires”, “penetrating heaven coolness”, “dragon and tiger joined in battle” and so on, implying the intensity of the needling (Cheng 1987).

According to the National Institutes of Health Consensus Conference on acupuncture in the USA “acupuncture describes a family of procedures involving stimulation of anatomical locations on the skin by a variety of techniques” (NIH Consensus 1998). In Merriam-Webster’s dictionary, acupuncture is defined as “an original Chinese practice of puncturing the body (as with needles) at specific points to cure disease or relieve pain (as in surgery)” (Merriam-Webster 2002). Another definition of acupuncture might simply be derived through the etymology of the word from the Latin roots *acus* (needle) and *punctura* (to puncture), implying that the term *acupuncture* should only be used when a needle penetrates the skin, which is the case in this thesis.

Acupuncture was not widely introduced as an alternative in Western medicine until the scientific basis of acupuncture analgesia (AA) began to be explored in the middle of the 1970s. The term AA was used for the rapid and strong, but short-term, pain relief that was required at surgery and produced by intense electro-acupuncture (EA) or strong, painful, manual manipulation of the needles (Mann 1974). In therapeutic acupuncture, used in clinical practice, the stimulation is mild compared to that aiming at AA (Mann 1974; Carlsson 2002). In Western medical acupuncture, treatment is based on orthodox clinical diagnosis and on the assumption of mechanically exciting receptors and nerve fibres in tissue. Different modes of needling are used in TCM as well in Western medical acupuncture. The variety of needling methods includes the number of needles, the depths of needle penetration, the diameter of the needles, whether manipulation of the needles is involved, and so on.

Different modes of acupuncture

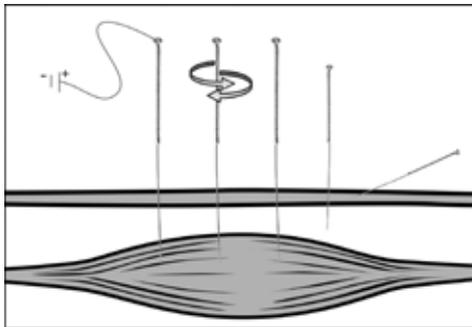


Figure 4: *Different modes of needle stimulation used in the trials. From left: electro-acupuncture (EA) (Study II), deep stimulation with manipulation of the (Deep) (Studies I-II, IV-VI), deep stimulation without manipulation (Mu) (Study IV), subcutaneous needle stimulation (SC) (Studies IV-VI), and extremely superficial needle insertion (SNI) used as near-placebo control (Study II).*

Manual acupuncture with needles inserted deep into tissue eliciting the *DeQi*-sensation is in the thesis hereafter named *deep acupuncture / deep stimulation* (Deep) (Figure 4). In *superficial acupuncture* needles are inserted superficially, to a depth of 5-10 mm (Baldry 2002), 4 mm (Macdonald, Macrae et al. 1983; Ceccherelli, Bordin et al. 2001) or 2 mm (Ceccherelli, Rigoni et al. 2002), i.e. the needle could be inserted into muscle tissue. In most reports, information on insertion depth in superficial acupuncture is missing, as well as whether or not the needles are being manipulated. Superficial acupuncture was found to be less effective and shorter-lasting than

Deep in the treatment of chronic pain (Lundeberg, Hurtig et al. 1988; Haker and Lundeberg 1990; Thomas and Lundberg 1994; Ceccherelli, Bordin et al. 2001; Ceccherelli, Rigoni et al. 2002). In this thesis the technique of inserting needles superficially, without penetrating muscle fascia and with no further manipulation of the needle, is hereafter called *subcutaneous needle stimulation* (SC). Extremely superficial insertion of the needle, without any manipulation, was used as control in one study and named *superficial needle insertion* (SNI). This mode of needling resembles, but is not identical to *minimal acupuncture*, which refers to superficial insertion of needles ~1-2 mm and slightly

manipulated (Lewith and Vincent 1998). Minimal acupuncture, recommended as placebo control in acupuncture trials, was recently shown to be equal effective as EA for the treatment of anterior knee pain (Naslund, Naslund et al. 2002)

Low-frequency EA causing muscle contractions is the mode of stimulation subjected to most research, especially in experimental pain models (Han 2003). Both larger and longer lasting analgetic effects were found to follow high intensity low-frequency EA compared to low intensity high- frequency EA (Romita, Suk et al. 1997). Furthermore, EA combined with manipulation of the needles had a larger analgetic effect than EA only (Kim, Min et al. 2000). Stimulation intensity differs between experimental animal research on pain thresholds, using relatively strong intensity, and clinical therapeutic EA, eliciting non-painful muscle contractions around the needle. The analgesic effect of EA was proposed to be more effective than Deep in experimental settings (Ulett, Han et al. 1998), and to be more long-lasting in chronic pain (Lundeberg, Hurtig et al. 1988; Thomas and Lundberg 1994). However, in a recent study on chronic low back pain, Deep was equally as effective as EA (Carlsson and Sjölund 2001).

In the clinical setting, various modes of stimulation may underlie different responses, such as salivary flow rate (Blom, Dawidson et al. 1992; Dawidson, Blom et al. 1997), peripheral blood flow (Jansen, Lundeberg et al. 1989; Blom, Lundeberg et al. 1993), ischaemic flap survival (Jansen, Lundeberg et al. 1989) and chronic pain (Lundeberg, Hurtig et al. 1988; Thomas and Lundberg 1994).

Possible mechanisms

Activity in afferent nerves caused by somatic stimulation has been demonstrated to modulate spinal and supraspinal reflex mechanisms, thereby influencing pain sensitivity, autonomic, hormonal and immune functions, muscle tone and to trigger peripheral events in the tissue (Melzack and Wall 1965; Lee, Chung et al. 1985; Budgell and Sato 1996; Kimura and Sato 1997; Sato, Sato et al. 1997). Different receptors, nerve fibres and neural structures will be activated to various degrees, depending on the strength, or dose, of the somatic stimulation, giving rise to different modulating mechanisms and responses. Generally, effects of gentle stimulation, such as brushing the skin, inhibits sympathetic outflow, while the immediate effects of noxious stimulation increases sympathetic outflow (Sato, Sato et al. 1997) .

The mechanisms of action of therapeutic acupuncture remain largely unknown, but knowledge regarding acute effects is extensible increasing from neurophysiological and neuropharmacological research.

Supraspinal and spinal levels

It is suggested that spinal and supraspinal effects of acupuncture primarily involve activation of thin myelinated A δ , or Group III, and possibly unmyelinated C, or Group IV, primary afferents from free nerve endings in the

skin or from high or low threshold mechanoreceptors (ergoreceptors) in muscle (Chang 1978; Han and Terenius 1982; Wang, Yao et al. 1985; Andersson 1993; Bowsher 1998). An abundance of information has accumulated concerning the neurobiological mechanisms of acupuncture in relation to both neural pathways and neurotransmitters and hormonal factors that mediate autonomic regulation and pain relief (Ma 2004).

Early experimental studies indicate that AA is mediated by endogenous opioid peptides via mechanisms at hypothalamic and brain stem levels, such as the periaqueductal grey and the nucleus raphe magnus (Chang 1978; Han and Terenius 1982; He 1987). Low-frequency EA is suggested to produce the most powerful segmental and extra segmental inhibitions of pain and modulations of the sympathetic system and autonomic functions (Thoren, Floras et al. 1990; Andersson 1993; Lee and Beitz 1993; Lovick, Li et al. 1995; Sandkuhler 1996). Different frequencies of EA are also suggested to activate different peptidergic substances in the central nervous system which may elicit profound physiological effects (Wang, Mao et al. 1990; Lee and Beitz 1993; Han 2003; Ma 2004). Special interest has been taken in β -endorphin, which is important in the control of pain (Basbaum and Fields 1984) and in the regulation of blood pressure (Holaday 1983) and body temperature (Olson, Olson et al. 1991). EA-induced increase in pain thresholds is only partially reversed by the opioid antagonist naloxone, suggesting that there are both opioid and non-opioid systems controlling input to the pain pathways (Andersson 1993). Other endogenous substances related to EA involve for instance monoamines (Han 1986), oxytocin (Uvnäs-Moberg, Bruzelius et al. 1993) and NPY (Bucinskaite, Lundeberg et al. 1994).

β -endorphin is also released into the blood stream from hypothalamus, via the pituitary, by EA (Andersson and Lundeberg 1995). This may indicate a stress reaction in response to EA. Notably, however, most experimental research on immediate and short-lasting central effects of acupuncture is performed with high-intensity EA in animals and conclusions regarding underlying mechanisms cannot automatically be applied to therapeutic acupuncture (Carlsson 2002).

Recent evidence has shown that nitric oxide (NO) may play an important role in mediating cardiovascular effects and analgesia in response to EA through the gracile nucleus–thalamic pathway (Ma 2004). NO in the gracile nucleus was suggested to play an inhibitory role in central cardiovascular control through regulation of somato-sympathetic reflexes and that these effects could contribute to the therapeutic effects of acupuncture (Ma 2004).

Three principles of endogenous antinociception have been proposed (Sandkuhler 1996). 1) supraspinal descending inhibition (Basbaum and Fields 1984), 2) propriospinal heterosegmental inhibition (Sandkuhler, Chen et al. 1997) and 3) segmental spinal inhibition (Melzack and Wall 1965). The two first mechanisms are proposed to be involved in the pain relieving effect of acupuncture, whereas the last probably plays a minor role.

1. Descending control from the periaqueductal grey in the midbrain is mediated via excitatory connections to serotonin-containing neurones of the nucleus raphe magnus of the medulla and NA-containing neurones of the nucleus locus coeruleus in the brainstem (Basbaum and Fields 1984). The release of NA and serotonin, via enkephalinergic interneurons, inhibits the firing of substantia gelatinosa cells in Lamina II of the spinal dorsal horn, thus preventing C-fibre nociception throughout the spinal cord being further transmitted. Multiple, parallel, and possibly independent descending pathways mediate inhibition of spinal nociception by environmental stimuli, such as acute stress and long-distance running and by conditioning stimuli of peripheral tissue, such as acupuncture (Basbaum and Fields 1984).

2. Propriospinal heterosegmental neurones are described to inhibit noxious responses (Sandkuhler, Chen et al. 1997). This system can be activated by heterosegmental, conditioning A δ -stimulation or by descending supraspinal pathways from the brainstem, leading to a strong and long-lasting depression of nociceptive information over several segments in the spinal cord. The long-term depression of nociceptive information may be involved in the long-lasting segmental antinociception of non-painful acupuncture, evoking low-frequency impulses in A δ fibres (Sandkuhler, Chen et al. 1997).

3. An afferent-induced segmental spinal form of antinociception involving A β fibres has since long been described (Melzack and Wall, 1965). This theory proposes that GABA-ergic interneurons in the substantia gelatinosa of the dorsal horn regulate the input of large and small fibres to Lamina V cells, serving as a gating mechanism. This pain control is strictly segmental organised and does not outlast the time of conditioning stimulation (Sandkuhler 1996).

Peripheral level

Peripheral level effects of acupuncture include events that are principally attributed to the release of neuropeptides from peripheral nerve endings upon stimulation of A δ and C-fibres (Andersson 1997; Lundeberg 1999). Local release of sensory neuropeptides, such as CGRP, substance P and opioids, is suggested to have a trophic role in the maintenance of tissue integrity and the repair process in response to tissue injury (Maggi 1991) and to possess anti-inflammatory actions (Hsieh, Choi et al. 1996). It has been shown that nutritive flow, capillary growth and proliferation of endothelial cells (angiogenesis) are increased by electrical stimulation of the rat calf muscle (Hudlicka 1998).

CGRP is a neuropeptide with highly potent vasodilator (Holzer 1992; Brain 1997) and pro-inflammatory effects (Brain 1997). However, in low doses CGRP has been shown to possess potent anti-inflammatory actions (Raud, Lundeberg et al. 1991) and was suggested to function as an endogenous anti-inflammatory agent (Raud, Lundeberg et al. 1991; Brodda-Jansen 1996).

Opioid receptors have been demonstrated on peripheral terminals of A δ and C-fibres and which increase in number during inflammation (Stein and Yassouridis

1997). In inflamed tissue opioid peptides (endorphin, enkephalin, dynorphin), produced by immune cells have been discovered. Upon release, these opioid peptides interact with their receptors on nociceptive neurones to produce analgesia.

By these mechanisms, acupuncture may be of importance in pain relief and tissue healing through the stimulation of nociceptors.

Psychological mechanisms

Acupuncture is suggested to induce an increased sense of well-being, calmness and improved sleep in many patients (Andersson and Lundeberg 1995; Carlsson and Sjölund 2001; Odsberg, Schill et al. 2001). In chronic pain patients symptoms of depression and trait anxiety were ameliorated (Dyrehag 1998) and depressed patients were improved (Luo, Meng et al. 1998) after low-frequency EA. The mechanisms behind the psychological effects of acupuncture may be attributed to β -endorphin and oxytocin, which are important in the control of pain, and well-being (Uvnäs-Moberg, Bruzelius et al. 1993; Uvnäs-Moberg 1998). Antidepressive and sedative effects of EA may also be attributed to increased synthesis and release of monoamines (serotonin, adrenaline) (Han 1986) and neuropeptides (Bucinskaite, Theodorsson et al. 1996). Involvement of limbic structures in the mechanisms of EA may also be important for affective behaviour.

Cortical effects of acupuncture include physiological / biological events evoked by psychological factors, and referred to as placebo effects or non-specific responses. The psychological factor is suggested to be particularly important in treatments which rely on endogenous modulation of functions in which psychological factors are integrated (Andersson and Lundeberg 1995). Several lines of evidence indicate that some types of placebo activate endogenous opioid systems (Levine, Gordon et al. 1978; Benedetti, Amanzio et al. 1995; Benedetti 1996; Benedetti and Amanzio 1997), although non-opioid mechanisms can play an important role in some situations (Grevert, Albert et al. 1983). Placebo analgesia related to expectation is suggested to be mediated via endorphin systems (Levine, Gordon et al. 1978; Grevert, Albert et al. 1983; Benedetti 1996), thus sharing, at least in part, same endogenous mechanisms as EA, whereas analgesia related to conditioning may be non-opioid mediated. It has been shown that opioid systems can be activated by both general and local placebos, indicating, that the expectation-induced placebo response is highly spatial-specific, requiring a cognitive component, i.e. spatial attention (Benedetti, Arduino et al. 1999). Furthermore, verbally induced instructions was found to influence unconscious physiological functions, such as hormonal secretion, and conscious physiological processes such as pain and motor performance, differently (Benedetti, Pollo et al. 2003). The authors suggested that placebo responses may be mediated by conditioning when unconscious physiological functions are involved.

A number of studies have supported the suggestion that cholecystokinin (CCK) may function as an antagonist to morphine and EA-analgesia and that low content of CCK in the central nervous system may be related to high analgesic response to EA in the rat (Han, Ding et al. 1985; Tang, Dong et al. 1997; Zhang, Li et al. 1997; Lee, Han et al. 2003). In both human and animals increased concentrations of CCK have been found during acute stress and anxiety (Harro, Vasar et al. 1993), which might explain the finding of lower pain relieving effect in chronic pain patients who experienced stress or anxiety during EA stimulation (Widerström-Noga 1993).

Benedetti (1996) also found that CCK antagonists are capable of potentiating the placebo analgesic effect, supporting the involvement of endogenous opioids in placebo analgesia. Recently, using PET technique, related neural mechanisms in the brain were demonstrated both in placebo-induced analgesia and opioid analgesia (Petrovic, Kalso et al. 2002), further supporting the suggestions of shared mechanisms in the brain.

Vascular effects of acupuncture

Both general and local vascular effects of acupuncture are proposed (Andersson 1997). Changes in central sympathetic tone result in general effects such as changes in heart rate and blood pressure.

Long-term EA is suggested to affect cardiovascular function by central modulation of sympathetic outflow (Yao 1993; Andersson and Lundeberg 1995), as evidenced by profound post-stimulatory reduction in arterial pressure and sympathetic nerve activity after long-term low frequency EA-like stimulation of the sciatic nerve in rats (Yao 1993). However, in healthy humans blood pressure did not decrease in response to 30 minutes of EA (Knardahl, Elam et al. 1998). With Deep, a transient increase in muscle sympathetic nerve activity was shown in humans at each needle manipulation (Sugiyama, Xue et al. 1995), and both Deep and EA induced initial short-term responses of a cool sensation and decrease in skin temperature, interpreted as sympathetic activation (Ernst and Lee 1985; Ernst and Lee 1986). This response was followed by a long-lasting warm effect, interpreted as a reduction in sympathetic activity. Direct stimulation of sympathetic efferent nerve fibres, however, produced vasoconstriction only, resulting in decreased blood flow to hindlimb skeletal muscles (Noguchi et al., 1999).

In experimental rat studies, similar skin blood flow increase and healing of musculocutaneous flaps were found after local acupuncture and injections of CGRP (Jansen, Lundeberg et al. 1989; Jansen, Lundeberg et al. 1989). In patients with xerostomia, associated with Sjögren's syndrome, increased skin blood flow overlying the parotid glands was found after Deep (Blom, Lundeberg et al. 1993) and the content of CGRP in saliva was increased (Dawidson, Angmar-Mansson et al. 1999). The skin blood flow increase in these studies was suggested related to the release of vasodilator substances, from peripheral

terminals of afferent nerves, or to interactions with sympathetic vasoconstrictor neurones.

Skeletal muscle microcirculation in rats was shown to increase in response to short bursts of electrical stimulation of dorsal root afferents, independently of sympathetic activity (Porszasz and Szolcsanyi 1994; Sato, Sato et al. 2000), or in response to stimulation of peripheral nerves (Loaiza, Yamaguchi et al. 2002). Muscle microcirculation and arterial diameter showed an intensity-dependent response relationship with larger increases at higher intensities, and increased blood pressure and heart rate as a response to sympathetic reflexes. The muscle blood flow increase persisted after selective and / or simultaneous α - and β -adrenergic blockade, suggesting that the blood flow response was not only a passive consequence of the elevated BP (Loaiza, Yamaguchi et al. 2002). Blood flow increase was also achieved in the rat vasa nervorum of the sciatic nerve following electrical stimulation of dorsal roots or of the saphenus nerve (Sato, Sato et al. 1994; Hotta, Sato et al. 1996). It was concluded in these studies that CGRP from afferent nerve terminals substantially contributes to the induced muscle and nerve vasodilatation. In support of this, release of CGRP into rat skeletal muscle was found following high threshold electrical stimulation of afferent fibres in the dorsal roots of rats (Sakaguchi, Inaishi et al. 1991).

Non-invasive measurement of blood flow

Ultrasound Doppler measures blood velocity in vessels to a specific region (Gill 1985). The principle of Doppler ultrasound uses an ultrasonic beam directed at a blood vessel in order to diagonally intersect it. Only sound reflected back by moving particles (red blood cells) is shifted in frequency. This frequency shift (in Hz) is proportional to the blood cell velocity. In order to estimate the blood flow from blood velocity the vessel diameter must be known. This is determined also with ultrasound Doppler with an acceptable accuracy in larger vessels, such as the femoral artery (Radegran 1997). However, the technique gives limited information about local muscle blood flow.

Laser Doppler flowmetry (LDF) is mostly used for non-invasive measurement of skin blood flow (Nilsson, Tenland et al. 1980). The technique is based on Doppler shift and on the frequency broadening of monochromatic light scattered in moving red cells. Light scattered in static structure remains unchanged in frequency. Shifted and un-shifted light is mixed on the surface of the photodetector, which after processing, gives an electrical output signal that is related to the perfusion as average blood cell velocity times the number of red blood cells. This method collects velocity data of a volume of 1 mm³ to a depth of approximately 1 mm. However, further development using the LDF technique has allowed blood flow to be measured in local muscle tissue by inserting a fibre optic probe into the muscle (Salerud and Oberg 1987). One drawback of this modality is, however, the trauma caused by insertion of the

optic fibre, which may affect the blood flow. The method is also prone to movement artefacts.

In *photoplethysmography (PPG)* light from a light source, such as a light emitting diode (LED), is directed towards the skin and this light is absorbed and scattered in the tissue. A small amount of this scattered light is received by a photodetector (PD) placed for example adjacent to the LED (reflection mode). Variations in the PD signal are related to changes in blood perfusion and blood volume in the underlying tissue (Challoner 1979; Kamal, Harness et al. 1989). The PPG signal consists of an AC and a DC component. The AC component is synchronous with the heart rate and corresponds to the pulsatile part of the blood flow. The amplitude of the AC component depends both on the pulsatile pressure (Larssen, Harty et al. 1997), the pulsatile blood flow (Challoner 1979) and the number of blood vessels in action for blood supply, in a complex way. The DC component of the signal varies slowly and reflects variations related to changes of total blood volume of the examined tissue (Challoner 1979), variations associated with vasomotion, the baroreflex loop, thermoregulation and with respiration. In the latter case there are slow variations on the venous side (Bernardi, Radaelli et al. 1996) and on the arterial side due to ventilatory changes in intrathoracic pressure (Larssen, Harty et al. 1997) and also slow variations due to respiratory sympathetic activity (Macefield and Wallin 1995). PPG has mainly been used to non-invasively monitor skin blood flow especially during and after transplantation surgery. The technique is also used in pulse oximeters for monitoring the arterial oxygen saturation (SpO_2) during anaesthesia and in the intensive care unit (Tremper and Barker 1989).

The PPG technique is now in progress for continuous non-invasive monitoring of blood flow and oxygen saturation at different vascular depths. The depth discriminating ability is mainly based on an appropriate combination of optical wavelengths and distance between the light source (e.g. a LED) and a PD. Different optical probes and techniques have been developed for visualising veins at a depth of 3mm from the surface (Fridolin, Hansson et al. 2000), monitoring of blood perfusion in the tibial anterior muscle (Zhang, Lindberg et al. 2001) and fetal oxygen saturation (Zourabian, Siegel et al. 2000). Custom-designed probes have been used, for instance, for studies of blood perfusion at enhanced intramuscular pressure (Zhang, Styf et al. 2001).

PPG is known to mirror larger measurement depths compared to the laser Doppler technique but this also depends on probe configuration and wavelength used (Lindberg and Öberg 1991). However, when comparing PPG for measurement of muscle blood flow and invasive LDF at 632 nm (muscle) it can be assumed that PPG mirrors a blood volume that substantially exceeds that of LDF.

Trapezius myalgia

Trapezius myalgia (TM) is characterised by pain from the trapezius area, pain upon palpation of the trapezius muscle and a sense of stiffness in the neck during movement. The diagnosis is set by a standardised clinical examination (Ohlsson et al., 1994). The prevalence of TM, predominately in women, is significantly increased in occupational groups involving high repetitive or long static, low force, contractions and is also associated with psycho-social factors (Ljung and Friberg 2004; Punnett and Wegman 2004).

The pathogenesis of work-related TM is unclear, but it is proposed that muscle nociceptors may be sensitised and excited by the release of different metabolic products related to muscle function (Sjogaard, Lundberg et al. 2000). Work-related muscle pain may be triggered by complex sympathetic-somatosensory responses to multifactorial mental and physical stressors (Zukowska and Lee 2003).

Impaired microcirculation in the local trapezius muscle has been found in chronic cases of neck myalgia (Larsson, Bodegard et al. 1990; Larsson, Oberg et al. 1999). Both morphological and physiological analyses of capillary supply indicate that reduced oxygenation of the muscle could result in a modification of the structure and function of the mitochondria (Thornell, Kadi et al. 2003). As a consequence of decreased blood flow, metabolic processes requiring energy can be seriously comprised. Biopsy studies have shown various mitochondrial disturbances in Type-I fibres and a reduced capillarisation per fibre cross-sectional area, which could indicate an ongoing energy crisis (Kadi, Waling et al. 1998; Larsson, Bjork et al. 2000; Larsson, Björk et al. 2004). For instance, in the trapezius muscle swollen endothelial cells in capillaries (Lindman, Hagberg et al. 1995), moth-eaten fibres (Lindman, Hagberg et al. 1991) and ragged red fibres (Larsson, Bjork et al. 2000) are found. These changes are found in control subjects, as well, but the level of disturbance is higher in symptomatic subjects. Mitochondrial, microcirculatory and metabolic changes may sensitise muscle nociceptors (Bengtsson 2002).

In a recent study on chronic work-related TM, increased resting levels of algogenic substances were found in the trapezius muscle, correlating with muscle pain and reduction in pressure pain threshold (PPT) (Rosendahl, Larsson et al. 2004). In addition, findings of increased anaerobic metabolism were found, which indicate nociceptive peripheral processes in the trapezius muscle. Recently, hyperalgesia / allodynia was demonstrated in the area of referred pain, indicating central hyperexcitability in patients with chronic trapezius myalgia (Leffler, Hansson et al. 2002; Leffler, Hansson et al. 2003).

Fibromyalgia

The diagnosis of fibromyalgia syndrome (FMS) is based on the American College of Rheumatology (ACR) classification criteria (Wolfe, Smythe et al.

1990) and requires two criteria, one of which includes a history of widespread pain for at least 3 months, including axial pain plus pain of both right and left sides of the body and pain above and below the waist. The second criterium includes pain in 11 or more of 18 specified tender point sites on digital palpation with an approximate force of 4 kg (allodynia / hyperalgesia).

The pain in FMS is commonly perceived as arising from muscles, and there are typically one or two locations that are the major pain foci, although sites of pain often shift and fluctuate in intensity over days and weeks. A majority of FMS patients report pain and stiffness in neck-shoulder muscles, and a majority develop FMS from localised or regional muscle pain conditions (Henriksson 2003).

Both peripheral and central factors are thought to contribute in varying degrees to the expression of symptoms in FMS, and several physiological and psychological factors are thought to interact. The cause of the initial pain may not be the same in all patients or even at all pain sites within the same individual (Henriksson and Sørensen 2002) and the pain mechanisms may differ among individuals with FMS (Sørensen, Bengtsson et al. 1997), implying a heterogeneity and possibly subgroups of FMS patients (Hurtig, Raak et al. 2001). However, the common feature in FMS is abnormal central pain processing (Clauw and Crofford 2003).

Several lines of evidence indicate abnormal central nervous system processing of noxious stimuli among individuals with FMS (Lautenbacher, Rollman et al. 1994; Kosek, Ekholm et al. 1996; Graven-Nielsen, Aspegren Kendall et al. 2000; Mense 2000; Staud, Vierck et al. 2001; Banic, Petersen-Felix et al. 2004) and an abnormal endogenous inhibitory control (Kosek and Hansson 1997; Lautenbacher and Rollman 1997). Recent fMRI findings support the occurrence of augmented central pain processing in FMS (Giesecke, Gracely et al. 2004). A state of central hyperexcitability involves phenomena like hyperalgesia and allodynia, i.e. lower pain thresholds and pain in response to non-noxious stimulus, respectively, and expanded referred muscle pain areas (Mense 1994; Graven-Nielsen, Aspegren Kendall et al. 2000). A generalised non-modality-specific increase in deep and cutaneous pain sensitivity, also at sites with no spontaneous pain, is shown (Gibson, Littlejohn et al. 1994; Kosek, Ekholm et al. 1996; Sørensen, Graven-Nielsen et al. 1998). It is suggested that central hypersensitivity could be induced, in part, by a nociceptive barrage of impulses in primary afferent C-fibres from muscles, possibly caused by ischemia, and, when allodynia is established, also by impulses in A-beta fibres (Bendtsen, Norregaard et al. 1997). After induction, maintenance of the hypersensitive state may be independent of ongoing peripheral nociception (Arendt-Nielsen and Graven-Nielsen 2003). The changes in nociceptive neurones in the central nervous system are probably expressions of neuroneal plasticity.

Among peripheral physiological factors, hypotheses are proposed that focal changes in muscle blood flow may be of importance in the pathophysiology of

FMS, such as disturbance in the microcirculation in the trapezius muscle (Henriksson 1994; Bengtsson 2002). Non-specific morphological aberrations in the trapezius muscle are similar to those found in TM, as mentioned above. Suggestions are also put forward that a disturbed microcirculation could be due to an abnormal regulation of capillary blood flow, rather than morphological changes in the capillaries, i.e. involvement of dysfunction in the autonomic nervous system (Bengtsson and Bengtsson 1988; Bäckman, Bengtsson et al. 1988; Qiao, Vaeroy et al. 1991; Arroyo and Cohen 1993; Martinez-Lavin 2002). Recently, muscle metabolism studied by P-31 magnetic resonance spectroscopy showed abnormal metabolism in painful muscles of FMS patients under maximal work load, but normal at rest and under submaximal dynamic loading (Lund, Kendall et al. 2003). It was concluded that FMS patients seem to utilise less of the energy-rich phosphorus metabolites at maximal work despite pH reduction, are less aerobic suited and reach the anaerobic threshold earlier than healthy subjects. Changes in muscles such as mitochondrial, microcirculatory and / or metabolic changes can sensitise muscle nociceptors, leading to pain during work, but does not alone explain the ongoing widespread pain or allodynia (Bengtsson 2002).

There is no curative treatment in FMS and no strong evidence has emerged regarding any single intervention and a multidisciplinary approach is recommended (Kang, Ansbacher et al. 2002). A systematic review of acupuncture identified 7 studies that showed beneficial effects of acupuncture on FMS symptoms, however, the majority were inadequately controlled non-randomised trials and long-term follow-up of patients was not a part of any of these studies (Berman, Ezzo et al. 1999). The only high quality study showed positive short-term beneficial effects of EA on pain and other symptoms (Deluze, Bosia et al. 1992). In an uncontrolled study, increased blood flow and skin temperature was registered above tender points, as well as a reduction of the number of tender points after acupuncture (Spratt, Jeschonnek et al. 2000). Still another study showed most beneficial effects of acupuncture on neck-shoulder pain (Lautenschläger, Schnorrenberger et al. 1989)

Postmenopause and climacteric symptoms

The majority of perimenopausal women suffer from vasomotor symptoms such as hot flushes and episodic sweating, which have a negative effect on the woman's quality of life. Tiredness and impaired working capacity, impaired mood states and other psychological symptoms are common (Barton, Loprinzi et al. 2001). The symptoms mostly occur during the first years of postmenopause and subside after 4-5 years. However, in 10-15% of women the symptoms persist for more than 15 years (Berg, Gottwall et al. 1988).

The exact pathophysiology of hot flushes is not known (Barton, Loprinzi et al. 2001), but several hypotheses have been put forth, involving changes in endogenous opioids and in noradrenergic and serotonergic systems. Estrogens

stimulate the production of hypothalamic β -endorphin and a decrease in oestrogen production around the menopause results in low β -endorphin activity (Shoupe, 1987). Postmenopausal women with vasomotor symptoms are also suggested to have elevated central sympathetic activity (Freedman 2001). Both changes in sympathetic activity and serotonergic system are suggested to influence thermoregulation and hot flushes (Kronenberg et al., 1984; Freedman, 2001).

Some women perceive hot flushes as a minor nuisance, whereas in other women this symptom disrupts work, sleep or daily activities. Postmenopausal women with vasomotor symptoms were suggested to suffer from more psychological stress, measured in terms of life events, depression and anxiety, as well as from hypothalamic and metabolic symptoms compared with postmenopausal women with vasomotor symptoms not seeking medical advice, although the incidence of hot flushes are the same (Ballinger 1985). Compared with asymptomatic postmenopausal women, women with vasomotor symptoms who seek medical advice may also have a higher level of neuroticism, as well as lower stress-coping (Nedstrand, Wijma et al. 1998). The authors stated that it may not only be strictly biological factors that influence whether certain women suffer from vasomotor symptoms, or not, and to what degree these symptoms are experienced as distressing.

Hormone replacement therapy is the treatment most prescribed to postmenopausal women with vasomotor symptoms, but alternatives are needed for women who are unable to use hormonal therapy for medical reasons or do not want to use hormones, because of unwanted side-effects. Among American women aged 45-60 years, 80 % reported the use of non-prescription therapies (Kang, Ansbacher et al. 2002). Acupuncture is one of a number of alternative treatments, which has gained much interest. However, a recent review on the use of alternative and complementary medicine in postmenopausal women concluded, that there is insufficient data to support the use of any alternative therapy for this purpose (Kang, Ansbacher et al. 2002).

Since hot flushes may be caused by low β -endorphin activity, EA was hypothesised as an effective treatment for hot flushes. EA was reported to induce beneficial effects on vasomotor symptoms in postmenopausal women, however, not superior to extremely superficially inserted needles, acting as a near-placebo (Wyon 2002).

AIMS OF THE STUDY

Overall aim

The overall aim of this thesis was to elucidate and investigate psychophysiological aspects and effects of acupuncture and needle stimulation. The emphasis was on the effects of needle stimulation on local muscle blood flow in healthy subjects and patients suffering from chronic muscle pain. Evaluation of a new application of photoplethysmography (PPG) in non-invasive monitoring of muscle blood flow was also performed. The psychological aspects comprised the pain alleviating effects of manual acupuncture in FMS and effects of electroacupuncture (EA) on vasomotor symptoms and psychological distress in postmenopausal women. The effects of *acupuncture* were considered when investigating the results of a series of acupuncture treatments in a clinical context and the effect of *needle stimulation* was considered when results of single needle stimuli were evaluated in an experimental setting.

Specific aims

Study I

The aim of this pilot study, with data collected between 1987-1989, was to investigate short and long-term effects of manual acupuncture (Deep) on pain, and other common symptoms, in FMS. Acupuncture had just been accepted in the General Practice at this time and the general knowledge of its mechanisms or effects on chronic muscle pain was largely lacking. The purpose was thus to evaluate the pain relieving effect *per se* and the not quality of life aspect.

Study II

The aim of the second clinical study was to investigate short and long-term effects of EA on the total climacteric symptom intensity and distress experienced from the symptoms in postmenopausal women.

Study III

This methodological study aimed at evaluating a new application of photoplethysmography (PPG) in non-invasive monitoring of muscle blood perfusion.

Studies IV and V

These two experimental studies investigated the effects of different modes of needle stimulation on blood flow in the anterior tibial muscle and overlying skin in healthy subjects (HS) (Study IV) and FMS patients (Study V).

Study VI

Study VI aimed at investigating the effects on blood flow in the trapezius muscle and overlying skin of two modes of needle stimulation in HS, FMS patients and patients with work-related TM.

Ethics

The local Ethics Committee of the Health University in Linköping approved the studies and all subjects gave their informed consent to participation.

Settings

The studies were performed at the Pain and Rehabilitation Centre and Departments of Rehabilitation Medicine and Biomedical Engineering at the University Hospital, Linköping, Sweden.

MATERIALS AND METHODS

Subjects

Details of the different study populations are given in **Table 1**.

Table 1: Study design and subjects (n=163) participating in the trials in studies I-VI

Study	Design	Follow-up	No. of subjects		Sex		Age mean (SD)	Diagnosis
			All	In groups	Female	Male		
I	Clinical trials	6 months	9		9		45.0 (12.5)	FM
	Cross-over			9				
	manual acupuncture customary treatment			9				
II	RCT	6 months	28		28		54.4 (3.6)	PM
	EA			15				
	SNI			13				
III	Methodology		66				26.0 (3.1)	HS
	static contraction			9				
	liniment			16				
	signal depth			3				
	muscle depth			43				
	skin temperature			13				
U-Doppler	10							
IV	Needle stimulation		14		14		38.0 (12.4)	HS
	Blocks							
	SC			14				
	Mu			14				
	Deep			14				
Control	14							
V	Blocks		15		15		39.9 (10.8)	FM
	SC			15				
	Deep			15				
	control			15				
VI	Blocks		44		44		36.4 (6.6)	HS
	SC			19				
	Deep			19				
	Control			6				

Out of a total of 163 subjects, 128 subjects participated in 1 study, 27 subjects participated in 2 studies, 3 subjects participated in 3 studies, 4 subjects participated in 4 studies, and 1 subject participated in 6 studies. EA = electro-acupuncture; SNI = superficial needle insertion; SC = subcutaneous stimulation; Mu = deep muscle stimulation without manipulation of the needle; Deep = deep muscle stimulation with manipulation to evoke the *DeQi* sensation; FMS = fibromyalgia; PM = postmenopausal women, HS = healthy subjects; TM = trapezius myalgia. U-Doppler = ultrasound doppler

Study I

Ten consecutive female FMS patients were referred to the study from the outpatient Rheumatology Clinic at the University Hospital in Linköping. The

diagnosis was set according to the Yunus criteria (Yunus, Masi et al. 1981), however, all patients but one also fulfilled the ACR 1990 criteria (Wolfe, Smythe et al. 1990). The duration of symptoms ranged from 2 to 17 years with a mean of 8 years. All patients had previously had physiotherapy but none had individual physiotherapy treatment during the study.

Study II

Thirty women with postmenopausal vasomotor symptoms were recruited through advertisements in the local press and at gynaecological outpatient clinics to participate in a study investigating effects of EA on vasomotor symptoms.

Study III

A total of 66 healthy subjects from staff and students at the university Hospital in Linköping participated in the various experiments evaluating non-invasive monitoring of muscle blood flow.

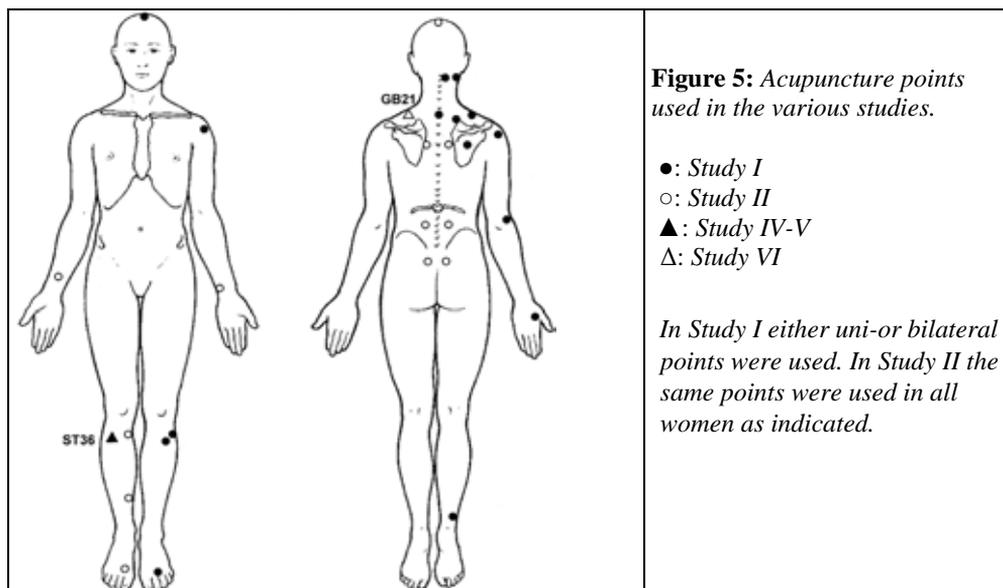
Studies IV, V and VI

Fourteen healthy, non-smoking, women were recruited from staff at the University Hospital in Linköping (Study IV) and 15 non-smoking female FMS patients were recruited from the Pain and Rehabilitation Centre at the University Hospital in Linköping (Study V). Nineteen healthy, non-smoking, females from staff and students at the University Hospital, and 20 FMS patients and 7 TM patients from the Pain and Rehabilitation Centre at the University Hospital in Linköping participated in Study VI. The FMS patients were diagnosed according to the ACR criteria (Wolfe, Smythe et al. 1990) and the TM patients according to the methodology described by Larsson et al. (2002).

Design and procedures - clinical studies

Study I

This was a cross-over designed study. The first five referred FMS patients were attributed to Group 1 and were given acupuncture treatment over a period of 2-3 months, two sessions per week during the first two weeks and then one treatment weekly. The subsequent five patients, Group 2, acted as non-treated control for 2-3 months. After this period, treatment was given according to Group 1. Six months after the end of treatment, Group 1 crossed over to become control. The patients were enrolled in the study for 12-14 months, including the 6 month follow-up period after treatment.



The treatment consisted of 10-14 sessions of Deep acupuncture. The patients indicated their most painful body area, which in all cases was within the neck-shoulder region. Within this local pain area, 4-6 needles were inserted. Another 2-4 needles were inserted distally to the elbow and knee. By variation in the number of needles and treatments, as well as the strength of needle manipulation, it was possible to slightly individualise treatment within the given framework. The most frequently used acupuncture points are shown in **Figure 5**. The patients lay comfortably with a blanket on and supported by cushions. Several of the patients became half asleep during the treatment.

Study II

This was a randomised placebo-controlled trial. At the first visit to the therapist the women were randomly allocated to either EA (n=15) or to a (near-) placebo control (n=15). Fourteen treatments were given twice a week during the two first weeks, and thereafter once a week for another 10 weeks. In the EA group the needles (0.30x30 mm) were inserted to a depth of ~ 5-20 mm, depending on location and underlying structure. The 12 acupuncture points, used at each session, are shown in **Figure 5**.

After the *DeQi* sensation was achieved at all points, the four needles in the lower back were attached to an electrical stimulator (IC-1107, ITO CO., LTD, Japan) giving low frequency alternating current stimulation (burst frequency of 2 Hz, with internal frequency of 80 Hz square wave pulses, pulse duration of 0.1ms) with an intensity strong enough to elicit non-painful muscle contractions around the needles. In the (near-) placebo group 12 needles (0.20x15 mm) were attached to the skin extremely superficially and up to 15 cm away from the

acupuncture points used in the EA group. Some of the needles fell off immediately when released and some during the session. The needles were left hanging loosely down from the skin, without any further stimulation. All needles were out of sight for the woman (**Figure 6**).



Figure 6: *Electroacupuncture (EA) and superficial needle insertion (SNI), the latter used as a near-placebo control, in Study II.*

All women were treated in a single room, lying comfortably in a lateral position with a blanket on and with pillows supporting the head and upper arm and leg. The therapist entered the room 2-3 times during the session to adjust the current intensity if needed, and otherwise to ensure that the women were comfortable. Many of the women became half-asleep during the sessions.

Assessments - clinical studies

Study I

Both objective and subjective variables were used. Objective variables included number of *tender points* (Yunus, Masi et al. 1981; Wolfe, Smythe et al. 1990), active *range of movement* in neck, active and passive range of movement in shoulders and *medication* intake. Visual analogue scales (VAS) (McCormack, Horne et al. 1988) were used for self-reported ratings of subjective variables: *general pain*, *local pain*, *sleep*, *muscle tension*, *psychological tension*, and *well-being*. The patients rated *global and local effects* of treatment using a 5-point category scale (0-4: 0 = no positive effect, 4 = pain-free). Local pain comprised the body region considered most affected by the patient and was head-neck-and shoulder region in all patients. The patients kept daily records of pain, sleep and medication intake at home in pre-printed diaries before and after treatment and control periods, respectively, and during 4th, 8th, 12th and 24th week after the end of treatment. Mean values for each week were calculated. Assessment of remaining variables was performed at visits to the clinic before and after control

and treatment periods, respectively, and at 4, 12 and 24 weeks after completion of acupuncture treatment.

Study II

Before start of treatment, after 4, 8 and 12 weeks of treatment, and at follow-up 3 and 6 months after completed treatment, the women filled in self-report scales at their visits to the Department of Obstetrics & Gynaecology.

Estimates of *general climacteric symptom intensity (GCSI)* and distress that the women experienced from the symptoms was rated by the women using VAS (McCormack, Horne et al. 1988) with the left endpoint indicating “no distress” and the right endpoint indicating “very severe distress”. The women's estimate comprised general climacteric symptoms, not just vasomotor symptoms *per se*.

Mood was measured using the self-administered Mood Scale. This scale is developed from earlier mood adjective checklists and consists of 6 dimensions, of which pleasantness, activation and calmness are considered to measure the bipolar dimensions of mood (Sjöberg, Svensson et al. 1979). Data from these dimensions were used for the analyses and presented as a total sum score with a min-max score 38-152, higher values indicating a better mood. The Mood Scale is developed in Sweden and tested for validity and reliability (Svensson, Persson et al. 1980).

General psychological well-being was measured using the Symptom Check List -90 (SCL-90) (Derogatis LR 1973). Originally, the SCL-90 was developed for measuring symptomatic behaviour of psychiatric outpatients. Five of the 9 dimensions in the SCL-90, measuring a domain of psychological well being, were selected for the present study, i.e. somatisation, depression, anxiety, hostility and interpersonal sensitivity. Remaining dimensions were considered to express psychiatric deviations, not relevant in this study. Thus, the scale was reduced from 90 to 50 items (SCL-50) and presented as a total sum score, lower values indicating a better general psychological well-being. SCL-50 has previously been used in studies on postmenopausal symptoms (Wijma, Melin et al. 1997).

Photoplethysmography – methodology

Probe design

The technique was based on specific assumptions according to **Figure 7**, which schematically illustrates the photon distribution in tissue containing both superficial and muscle compartments. A short distance between a green LED (560 nm) and a PD correlates to a short penetration depth due to the high absorption in skin (pigment) and blood (haemoglobin). This makes it possible to utilize 560 nm for measuring skin blood perfusion (Lindberg and Oberg 1991; Hales, Roberts et al. 1993; Futran, Stack et al. 2000). In contrast, a long distance

between a near-infrared LED (804 nm, 880 nm) and a PD enables deep penetration because the photons are multi-scattered in tissue (dermis, fat, collagen) at this wavelength and undergoes less absorption in blood.

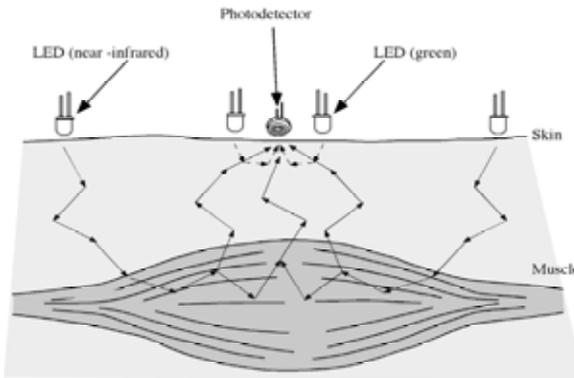


Figure 7: Schematic description of the photon propagation into tissue emerging from a green light and a near-infrared light source (LED in combination with different distances between source and a photodetector).

Specially designed optical probes according to **Figure 8 a-c** were used in the different studies. A probe consisted of 3 PDs, 6 green LEDs and 2 (a) or 3 (b) near-infrared LEDs (Studies III-V) or 4 PDs, 4 green LEDs and 2 near-infrared LEDs (c) (Study VI) placed in a special pattern and embedded in black coloured silicone rubber.

The optical probes, containing several LEDs and PDs, were developed to have the following specifications:

- The pulsatile signal, reflecting blood flow, is measured from a large area on the skin surface, which gives an integrated PPG signal from a large vascular volume. This integration partly compensates for spatial blood flow variations (Tenland, Salerud et al. 1983; Lindberg and Oberg 1991).
- blood flow is measured both superficially and deeper in muscle tissue making use of a special optical geometry and 2 different optical wavelengths: 560 nm, green light, and a centre-to-centre distance of 3.5 mm between LED and PD for monitoring blood flow at a depth of approximately 1-2 mm; 880 nm, near-infrared light, and a centre-to-centre distance of 20 mm between LED and PD (**Figure 8a**) (Study III, V and VI) and 12 and 22.5 mm (**Figure 8b**) (Studies III-V), respectively, for monitoring blood flow in the muscle tissue. In Study VI a specially custom-designed 2-channel optical probe was developed and optimised for measurement of blood flow in the trapezius and supraspinatus muscles (**Figure 8c**).

- the pulsatile PPG signal, reflecting the blood flow, was measured from a large vascular volume by using of several LEDs and PDs.

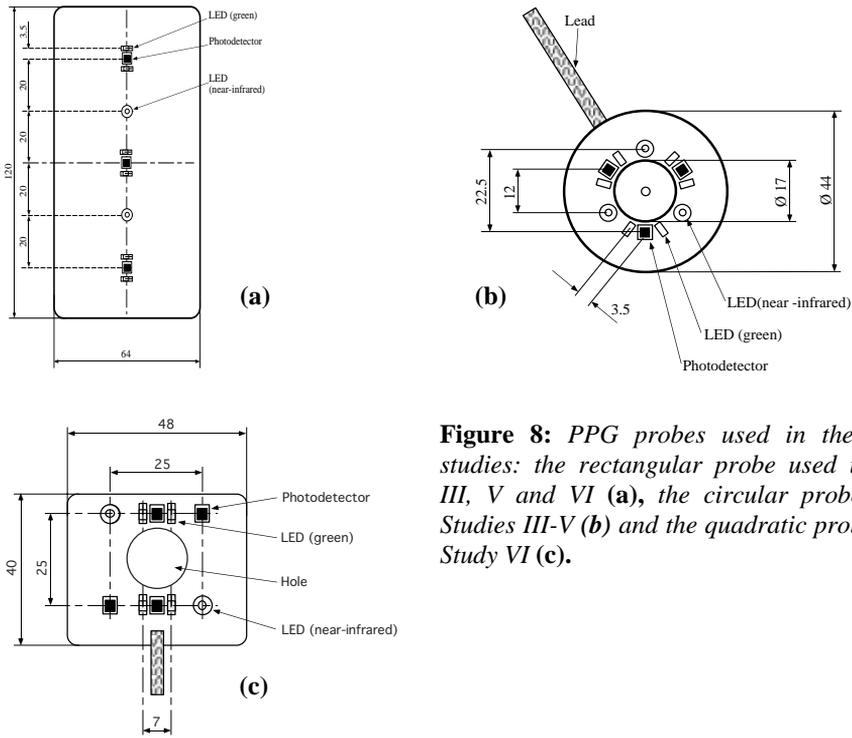


Figure 8: PPG probes used in the different studies: the rectangular probe used in Studies III, V and VI (a), the circular probe used in Studies III-V (b) and the quadratic probe used in Study VI (c).

The signals from each wavelength were simultaneously processed in an amplifier and stored on a laptop PC, and analysed afterwards. Blood flow was analysed as the mean value of the peak-to-peak value of the pulsatile PPG signal over 20-60 s.

In Study VI the infra-red LED used a wavelength of 804 nm to ensure that the blood flow signal was insensitive to variations in oxygen saturation. The centre-to-centre distance between the LEDs and the PDs was 3.5 mm and 25 mm for the wavelengths 560 and 804 nm, respectively.

The PPG instrument used in Study VI was a digital microprocessor-controlled system that could handle the two-channel sensor configuration. For each channel all LEDs were connected in series and the PDs were connected in parallel. In order to extract an AC PPG signal to work with, a DC portion (the compensating signal) was subtracted from the total signal and the remaining AC signal was amplified and then sampled by an Analogue to Digital-Converter (ADC). The compensating signal is the mean value of the AC PPG signal and is normally gained in a low pass filter (slow filter). If the amplified AC portion of the total PPG signal exceeds the input range of the ADC the cut off frequency of the low pass filter is increased (fast filter). This means that the system can respond to a fast change in the total PPG signal with minor signal distortion.

Experimental procedures - Study III

Static contraction

A post-contraction hyperaemic response was used to increase blood perfusion in the muscle. Blood perfusion was measured for 180 s in the biceps brachii muscle and overlying skin in 9 healthy subjects following a moderate static contraction for 60 s. Probe 2a was attached over the most prominent part of the muscle when contracting.

Liniment application

Liniment (Transvasin®) was applied on the skin surface midway between the lateral malleolus and transverse popliteal crease, approx. 2 cm lateral to the anterior crest of the tibia, in 16 healthy subjects in order to increase the skin blood perfusion by vasodilator activity (Fulton, Farber et al. 1959). Blood perfusion was measured in the anterior tibial muscle and overlying skin at the site of liniment application, using probe 2b. After the reference blood perfusion was established, the probe was removed and a minor amount of liniment was quickly applied to the surface of the PD. After replacement of the probe onto the same skin site, measurements of blood perfusion were continued for another 5 min.

In vivo determination of signal depth

The distance between the skin surface and the location of the anterior tibial muscle was measured at the most prominent part of the muscle, approx. 2-3 cm lateral to the anterior crest of the tibia, in 43 subjects using ultrasound Doppler.

The signal depth is defined as the depth from which some of the photons originate, and contribute to the PPG signal. In 3 healthy subjects a catheter (32 x 1.2 mm) was inserted into the anterior tibial muscle approximately parallel to the muscle fibres (Styf and Körner 1986). An optic fibre was then inserted into the plastic tube and connected to an optical Power Meter (POM) for recording the radiant power in the muscle. The PPG probe 2a was placed over the anterior tibial muscle above the fibre tip and the multi-scattered photons from deep inside the muscle was measured using the POM.

Temperature dependence during long-term recordings

Blood perfusion was measured in 13 healthy subjects at rest in order to investigate the influence on blood perfusion of temperature changes originating from changes in the local environment as well as local temperature regulation. A temperature sensor was positioned between the skin surface and the PPG probe. After application of the probe at the level of the lower part of the tibial tuberoses, approx. 2 cm lateral to the anterior crest of the tibia (i.e., acupuncture point ST 36 (Jenkins 1990)) (**Figure 5**), measurements of blood perfusion were performed for 30 min, using probe 2b. In a second step, 4 of the subjects participated in another 3 experiments, where only one of the LEDs at a time was

applied, either the green or near-infrared, or just the probe including the temperature sensor but with no LEDs turned on.

Comparison with pulsed Doppler velocimetry

Blood perfusion was measured in the tibialis anterior muscle in 10 subjects. Probe 2a was attached to the skin at the most prominent part of the muscle, approx. 2-3 cm lateral to the anterior crest of the tibia. As a reference, peak femoral blood flow (FBF) was monitored using pulsed Doppler velocimetry (ATL, HDI 5000, L 12-5 Philips, Germany), and determined from the spectra of the pulsed Doppler ultrasound signal. A flat probe was fixed to the skin over the artery 2-3 cm distal to the inguinal ligament. Peak femoral flow velocity and artery diameter were measured after repeated full range dorsi- and plantar flexion of the ankle for 1 min and the post-exercise hyperaemic response were followed for 5 min. Blood perfusion was simultaneously measured by application of the PPG probe over the anterior tibial muscle. This experiment was performed to elucidate similarities and differences between the two techniques.

Needle stimulation - methods

Studies IV and V

Three modes of needle stimulation were used on each subject on separate days: 1) subcutaneous needle insertion (1-3 mm) (SC); 2) deep needle (10-20 mm) insertion into the anterior tibial muscle (Mu); and 3) deep needle insertion into the anterior tibial muscle, immediately followed by twirling the needle in order to evoke the *DeQi* sensation (Deep). Mu was excluded in study V. The needle (0.30x30 mm) was inserted in the middle of probe 2b, perpendicular to the skin at the anterior aspect of the tibia, corresponding to acupuncture point ST 36 (**Figures 5 and 9**). A separate resting session with no needling was included as control. In Study V probe 2a was simultaneously used to monitor blood flow at the corresponding site on the contralateral side. After intervention, the needle was left for 20 min without further manipulation.

Study VI

Two modes of needle stimulation were performed at the upper part of the shoulder, corresponding to acupuncture point GB 21 (Jenkins 1990) (**Figures 5 and 10**).

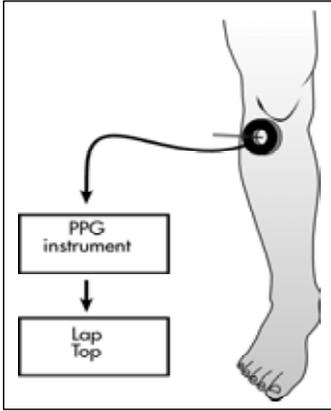


Figure 9: Application of the probe in Studies IV and V.

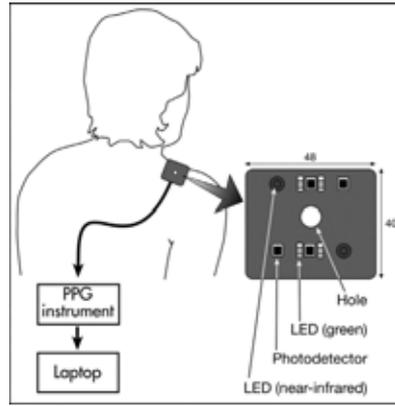


Figure 10: Application of the probe in Study VI.

The SC mode of stimulation consisted of inserting three 0.25x15 mm needles through the hole of probe 2c, perpendicular into subcutaneous tissue, and with no further manipulation. The Deep mode stimulation consisted of inserting one 0.30x30 mm needle obliquely, $\sim 45^\circ$ in dorsal direction, into muscle tissue ($\sim 10\text{-}15$ mm), immediately followed by manipulating the needle to achieve the *DeQi* sensation. The manipulation was repeated twice every 10th min. All needles were withdrawn after 20 min. Blood flow was recorded for 60 min after intervention, i.e. for another 40 min after needle removal. Probe 2a was simultaneously used to monitor muscle blood flow at the corresponding site on the contralateral side. Designs and procedures of Studies IV-VI are shown in **Figure 11**.

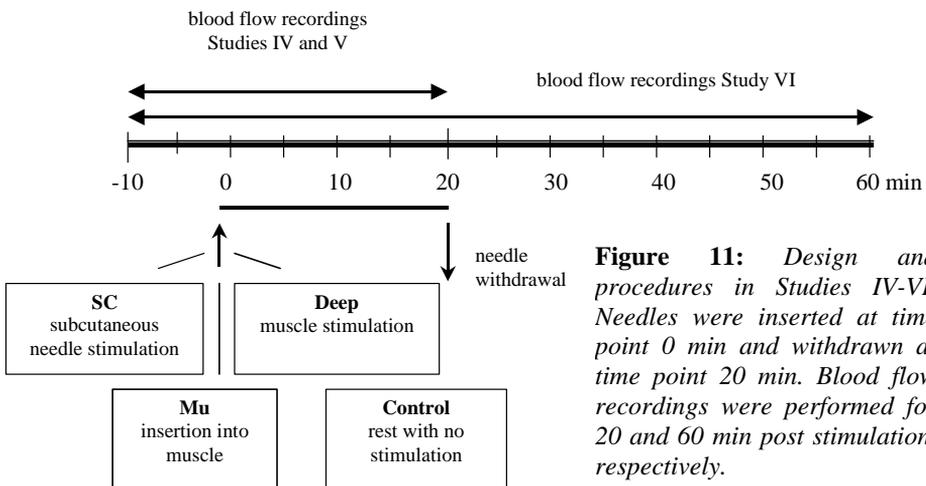


Figure 11: Design and procedures in Studies IV-VI. Needles were inserted at time point 0 min and withdrawn at time point 20 min. Blood flow recordings were performed for 20 and 60 min post stimulation, respectively.

Needle stimulation - assessments

Studies IV, V and VI

Blood flow recordings were performed intermittently, starting 10 min before intervention and throughout the trial.

Subjective experience of anxiousness about the intervention, and *pain* intensity and *discomfort* experienced from the intervention was estimated using VAS, with the left endpoint depicting “not at all” and the right endpoint “worst possible”. In Study VI the patients also rated ongoing general pain and local pain from each shoulder at the start of each trial.

Pressure pain thresholds (PPT) (Study VI) were measured bilaterally at the upper part of the trapezius muscle, using an electronic algometer (Somedic®, Sweden) (Persson, Hansson et al. 2000). Pressure algometry has been reported to mainly reflect pressure pain sensitivity of deeper tissues (Kosek, Ekholm et al. 1999). The device consists of a pistol grip and a rod with a pressure-sensitive strain gauge at the tip (area 1 cm²) covered with a 2-mm thick rubber pad and connected to a power supply, an amplifier and a display. The display shows pressure (in kPa) and a scale enables the examiner to keep a fairly constant rate of pressure force increase (here 20 kPa/s). The patient was instructed to press a handheld button, when perceiving pain instead of pressure or tenderness.

Active range of movement (AROM) of the neck (Study VI) was measured with the cervical range of motion instrument (CROM) (Peolsson, Hedlund et al. 2000). The device consists of a plastic frame, mounted over the bridge of the nose and ears of the subject, and equipped with two gravity goniometers and a compass attached to the frame. Forward flexion, extension, and bilateral lateral flexion and rotation AROM were measured and a mean AROM value was calculated and used in the analyses.

Statistics

The statistical packages Statview 5.1 (Abacus SAS Institute Inc. NC, USA) and SIMCA-P 10.0 (Umetrics AB, Umeå, Sweden) were used for the statistical analyses. Tables and figures are presented with mean (\pm 1 SD) or median (min-max) values. In study II median values and interquartile ranges were used. The non-parametric *Wilcoxon Matched-pairs signed-ranks Test* was used for pairwise comparisons within groups and the *Mann-Whitney U-test* for between-group comparisons. *Friedman’s test* was used for repeated measures of dependent variables and *Kruskal-Wallis test* for multiple comparisons of independent variables and, if significant, *Student-Newman-Keuls test* was used.

In studies I and VI, *principal component analysis* (PCA) was used. PCA can be viewed as a multivariate correlation analysis, which was performed using SIMCA-P, to analyse the relationships between variables and to detect if a number of variables reflect a smaller number of underlying components

(Eriksson, Johansson et al. 1999). Principal components with Eigenvalues > 2.00 were considered as nontrivial components. A component consists of a vector of numerical values between -1 and $+1$, referred to as loadings. The loading expresses the degree of correlation between the item and the component. A loading is obtained for each measurement variable included in the PCA model. Variables that have high loadings (with positive or negative sign) upon the same component are inter-correlated. We have considered loadings ≥ 0.25 in absolute numbers (i.e., irrespective of sign) to be high and therefore of interest. Items with high loadings (ignoring the sign) are considered to be of large or moderate importance for the component under consideration. A cross-validation method, which keeps part of the data out of the model development to assess the predictive power of the model, was used to test the significance of the components. Outliers were identified using the two methods available in SIMCA-P: 1) score plots in combination with Hotelling's T^2 (identifies strong outliers); and 2) distance to model in X-space (identifies moderate outliers).

In study I *partial least square regression* (PLS) was used for predictions of subjective evaluations of treatment outcome from base-line data. In contrast to multiple regression, PLS can handle correlated regressor variables (X variables) and missing values, and it does not require a high subject-to-variable ratio, i.e. more variables than subjects can be handled. In addition, several Y variables can be regressed simultaneously.

All tests were performed at the 5 % significance level.

SUMMARY OF RESULTS AND COMMENTS

Study I

Acupuncture was expected to primarily decrease pain intensity and secondly to relieve other common symptoms in FMS more than control. In general, significantly greater changes occurred during the acupuncture period than during the control period (**Table 2**).

Table 2: Result of statistical analyses of between-group and within-group changes in Study I

Variables	Control vs. acupuncture	Before vs. after control and acupuncture		Base-line vs. follow-up after acupuncture			
	<i>p</i>	control <i>p</i>	acup <i>p</i>	4 w <i>p</i>	8 w <i>p</i>	12 w <i>p</i>	24 w <i>p</i>
TP	0.03	0.05	0.03	0.04	-	0.04	ns
RoM SHA	0.04	ns	0.01	ns	-	ns	ns
RoM SHP	ns	ns	0.04	ns	-	0.05	ns
RoM NEA	ns	ns	ns	ns	-	ns	ns
MED	0.03	0.05	0.05	ns	0.04	ns	ns
Pain	0.01	ns	0.01	0.02	0.01	ns	ns
PLOC	0.01	ns	0.01	0.01	-	0.01	0.04
Sleep	0.05	ns	0.02	ns	0.05	ns	ns
MT	0.01	ns	0.01	0.02	-	0.02	0.05
PT	ns	ns	ns	ns	-	ns	ns
WB	0.05	ns	0.01	0.02	-	0.02	ns

TP=tender points; RoM SHA=active, and RoM SHP=passive, range of movement in shoulders; RoM NEA=active range of movement in neck; MED=medication; PLOC =local pain; MT=muscle tension; PT=psychological tension; WB=wellbeing; Base-line=before acupuncture. P-value is given if significant, ns denotes non -significant, - denotes not available.

Of the nine patients completing the study, seven patients (78%) reported considerable (>50%) decrease in ongoing pain after completion of treatment. Of these, three reported $\geq 75\%$ reduction in pain. The other four patients reported ~50-65% reduction in pain. In the assessment of global treatment effect, one-third of the patients rated very good effect (i.e. 3 and 4 on the category scale), one-third rated good effect (i.e. 2 on the category scale), whereas the remaining third reported more or less no effect (i.e. 0-1).

The ratings of global and local treatment effect were maintained at the 4-week, but not at 12-week follow-up. Local pain and muscle tension in neck-shoulder region was reduced throughout the 6-month follow-up period, whereas shorter and weaker effects were obtained regarding the general the complaints. Baseline values of sleep and well-being were found to best predict global outcome of acupuncture, in that relatively good sleep and well-being was associated with more positive effects, whereas general pain had less important predictive value.

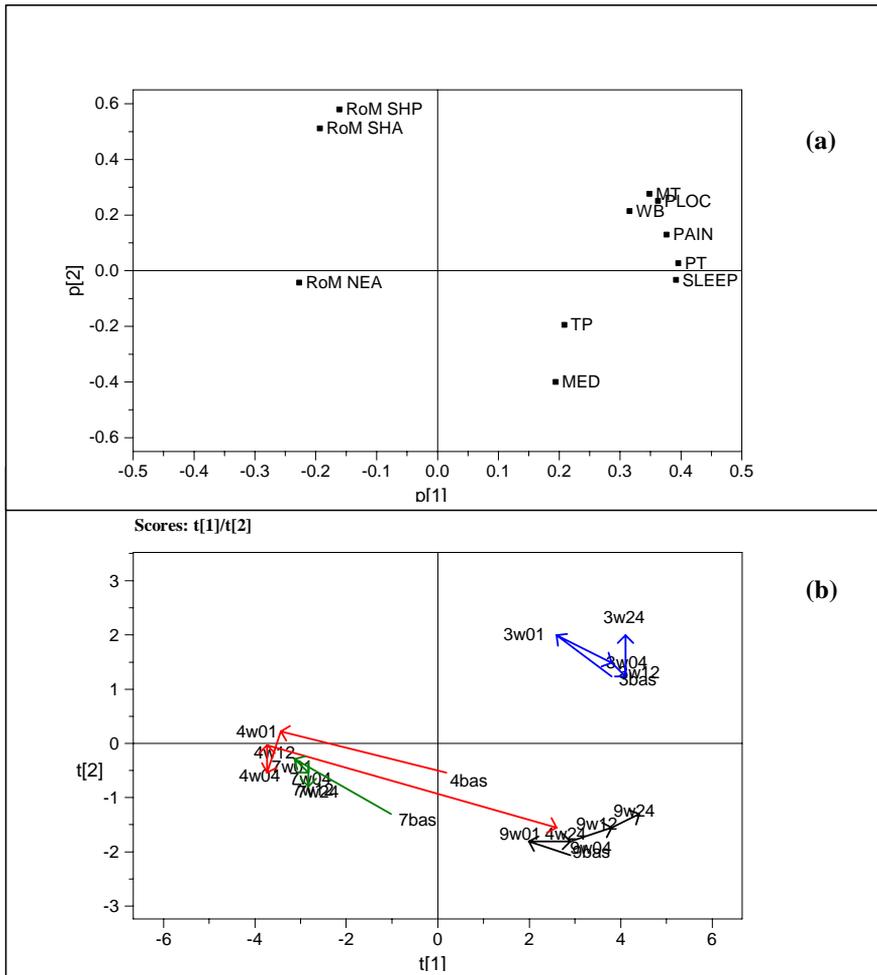


Figure 12: Principal component analyses (PCA) of the base-line period with the loading plot (i.e. denotes the relationships between variables). The two significant components are given. The first component ($p1$) explains most of the variance ($R^2=0.50$; Eigen value =4.47) when compared to the second component ($R^2=0.21$; Eigen value=1.89) (a). PCA using time series data. Four patients are shown in the score plot. Movement horizontally from right to left indicates improvements in variables mainly loading upon component $p1$ (i.e. sleep, TP, PLOC etc.). Movement vertically upwards indicates improvements in RoM NEA. 0 indicates base-line period, 1 indicates after end of acupuncture, 4, 12, 24 indicates follow-ups. For instance 9:24 indicates patient no 9 at 24th week of follow-up (b).

Two patterns of response patterns to treatment could be discerned, which are illustrated in **Figure 12**. After completion of treatment period all four patients improved. However, at follow-up patients 3 and 9 quickly returned to baseline level, whereas patients 4 and 7 remained improved at 3 and 6 months follow-up, respectively.

Comments

There is only one high quality placebo-controlled RCT on acupuncture (EA) in FMS, reporting considerable improvement after completion of treatment (Deluze, Bosia et al. 1992). Generally, the response pattern of the immediate effects in that study was similar to the present ones, i.e. with a small subgroup (25 %) responding extremely well, 50% responding reasonably well, while the remaining 25 % did not benefit at all. However, the study by Deluze (1992) lacked long-term follow-up. The finding of positive and long-term effects locally, i.e. on neck-shoulder complaints, in contrast to the more short-lasting effects on general FMS complaints was interesting. Similar results were found in the study by Lautenschläger (1989).

Study II

The hypothesis of EA being superior to a (near-) placebo control in decreasing psychological distress and experience of climacteric symptoms in postmenopausal women was not accomplished (**Figure 13 a-c**). Significant improvements were found on climacteric symptoms (**a**) and general well-being (**b**) in both EA- and the (near)-placebo groups during and at the end of the treatment period, as well as at 3 and 6-months follow-ups. No significant differences existed between the groups. Mood (**c**) improved in the EA group only, appearing at the end of the treatment period, and was significantly more improved in EA than control group at 8 and 12 weeks.

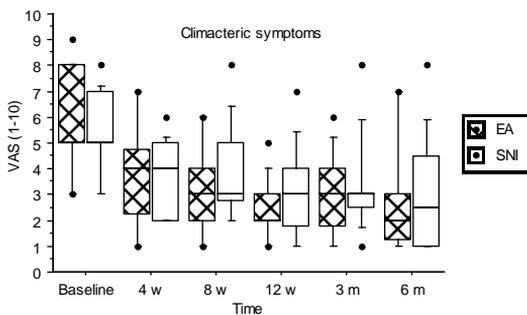


Figure 13a: Climacteric symptom intensity. All changes in both groups from baseline are significant at or below $p \leq 0.05$. No significant difference existed between the groups.

Median values with interquartile ranges, 10th and 90th percentiles and outliers are shown.

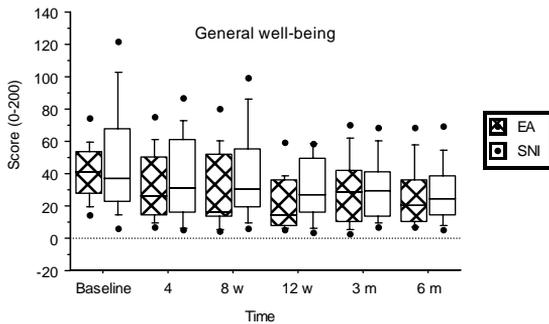


Figure 13b: General wellbeing.

All changes in both groups from baseline are significant at or below $p \leq 0.05$. No significant difference existed between the groups.

Median values with interquartile ranges, 10th and 90th percentiles and outliers are shown.

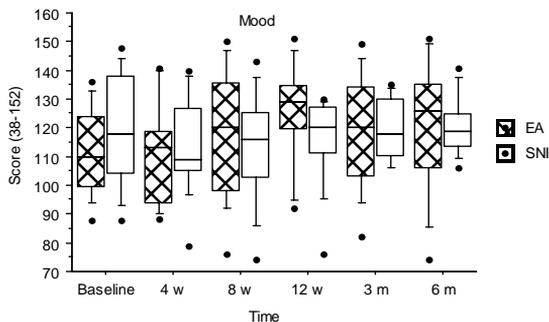


Figure 13b: Mood (c).

In the EA group significant improvement existed at 12 weeks and 3 months. The SNI group did not change significantly.

Median values with interquartile ranges, 10th and 90th percentiles and outliers are shown.

Comments

In contrast to Study I, this trial included a (near-) placebo control consisting of extremely superficially inserted small dimension needles, all of which were out of sight for the woman. Both groups were handled identically, implying equal amount of care, interest, attention and time spent with the therapist. Only the needling procedure *per se* differed between the groups. This result indicates considerable non-specific effects. The better result in the EA group on mood indicates that EA might have additional effects compared with the (near-) placebo control.

Study III

Static contractions and liniment

After a moderate static contraction a post-contraction hyperaemic increase in muscle blood perfusion, but not in skin blood perfusion, was found (**Figure 14a**). The application of liniment to the skin gave rise to an almost direct

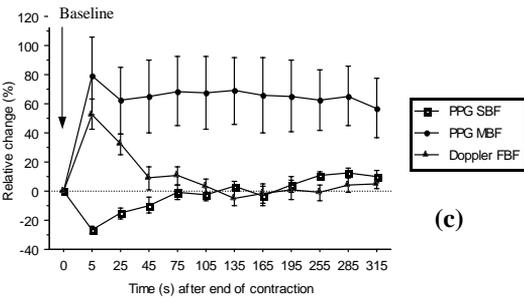
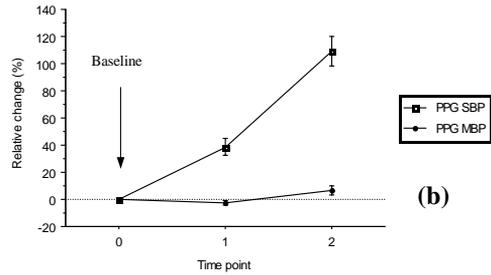
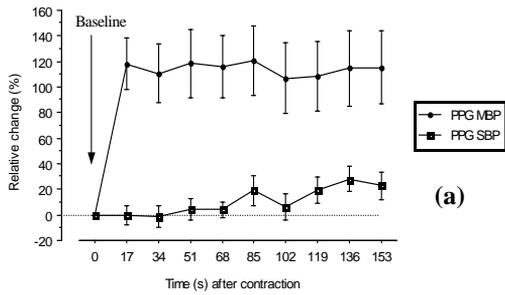


Figure 14: Relative changes in PPG_{SBP} (skin blood perfusion), PPG_{MBP} (muscle blood perfusion) and femoral blood flow (FBF) intermittently recorded for 60s after static contraction (a), liniment application (b) and dynamic contractions (c). Values (mean ± SE) are given as the percentage of the initial resting value (0%).

increase in skin blood perfusion, while muscle blood perfusion only showed an increase at the end of the measuring period (**Figure 14b**).

Comparison with pulsed Doppler velocimetry

Directly after dynamic contractions the post-exercise hyperaemia in the tibialis muscle was monitored both by PPG_{MBP} and ultrasound Doppler (**Figure 14c**). However, thereafter the relatively high blood flow level in PPG_{MBP} demonstrated a local blood flow enhancement, which was not monitored by the Doppler technique in the femoral artery. PPG_{SBP} exhibited a decrease directly after the contractions and thereafter stayed close to the resting value.

In vivo determination of signal depth

The mean distance between the skin surface and muscle fascia of the anterior tibial muscle was 5.4 mm (range 2.10–13.8 mm). The radiant power measured in the muscle tissue indicated that near-infrared light penetrates at least down to a vascular depth of 13.0 mm from the skin surface. The radiant power emerging from the skin surface and reaching the PD was found to be in accordance with previous measured values at the skin surface, using a POM. One subject also performed dynamic contractions for 60 s, after which the radiant power decreased by 12 % over 60 s, indicating an increase in blood volume in the muscle.

Temperature dependence during long-term recordings

Application of the probe gave rise to a mean increase in skin temperature of 2.5 % during the initial 10 min. When the LEDs were turned on, the temperature slope was further enhanced, and both PPG_{SBP} and PPG_{MBP} exhibited an increase of approximately 10 % over 5 min. At approximately 25 min PPG_{SBP} and PPG_{MBP} started to increase further, whereas the skin temperature curve, T_{skin} , flattened out more and more.

In order to distinguish between the influences of 560 and 880 nm, experiments were repeated in 4 subjects turning on the two types of LEDs, and the probe, separately. When the green LEDs were turned on, an increase in PPG_{SBP} was obtained, whereas near-infrared light only was followed by a decrease in blood flow measured by PPG_{MBP}. The rise in skin temperature was more influenced by the green LED than the near-infrared one. The application of the probe only, with no LED turned on, initially gave to an increase in skin temperature, T_{skin} (probe), but from 10 min onwards there was only a minor further increase in skin temperature.

Comments

Post-exercise hyperaemia is a well-known phenomenon after both static and dynamic contractions (Bangsbo and Hellsten 1998) and was accordingly detected in these trials. Liniment is known to increase skin blood perfusion (Fulton, Farber et al. 1959) and in this trial gave rise to an almost direct increase in skin blood perfusion, while muscle blood perfusion only increased towards the end of the measuring period. The rise in temperature, measured between the skin surface and the probe, is probably explained by inhibited convection. When the LEDs were turned on, the distributed heat gave rise to vessel dilatation and a corresponding increase in blood perfusion. The substantial increase in blood perfusion after 25 min was probably due to a temperature regulation effect (Svanes 1980). The green LED was found to influence muscle blood flow more than the near-infrared during long-term monitoring. The experiment, using PPG and pulsed Doppler velocimetry simultaneously, elucidated both similarities and differences between these techniques, the former measuring local blood perfusion and the latter measuring arterial inflow to the whole limb.

Taken together, the results of these experiments indicate that PPG could be used in non-invasive monitoring of muscle blood perfusion.

Studies IV, V and VI

Blood flow changes are presented as area under curve (AUC), or mean AUC, over 5 min and presented in relation to control, i.e., a resting situation, or between the different modes of stimulation. Pre-5 refers to 5 min prior to intervention. T:1, T:2, T:3, and T:4 refer to first 5 min, 5-20 min, 20-40 min, and 40-60 min, respectively, after intervention. Baseline is at 0 s and refers to the mean over 60 s immediately prior to intervention.

The tibialis anterior muscle

In both FMS and HS the deep mode of needle stimulation (Deep) induced greater skin and muscle blood flow increases than control and no differences existed between groups. In HS, the subcutaneously inserted needle (SC) did not increase skin blood flow and muscle blood flow was only transiently increased for one or two min, and not enough to reach significance at T:1. In FMS, in contrast, SC induced an increase in skin as well as muscle blood flow, although Deep was superior to SC. The latter mode of stimulation induced significantly greater skin as well as muscle blood flow increases in FMS than in HS (**Figure 15**).

Manipulating the needle after insertion into muscle tissue in order to achieve the *DeQi*-sensation (Deep) in HS induced greater blood flow increase than only inserting the needle (Mu), which in turn induced greater blood flow increase than SC (Study IV). No differences existed in blood flow change between the stimulated and non-stimulated leg at control or at the pre-5 periods.

VAS ratings of anxiety, pain and discomfort with the needling are shown in Table **Table 3**.

Comments

The results of Deep being superior to SC in increasing skin blood flow are supported by both animal (Jansen, Lundeberg et al. 1989; Jansen, Lundeberg et al. 1989) and human (Blom, Lundeberg et al. 1993) studies. Muscle blood flow increase has been shown in rats in response to acupuncture-like electrical stimulation, and measured using invasive laser Doppler-technique (Noguchi, Ohsawa et al. 1999; Sato, Sato et al. 2000).

However, up to now there are no reports on blood flow changes in human muscle following somatic afferent stimulation, such as acupuncture. An interesting finding was the difference between HS and FMS in response to SC, in that FMS patients showed significantly increased skin as well as muscle blood flow, in contrast to HS. In FMS, a tendency toward greater muscle blood flow increase was also shown with Deep, compared to HS.

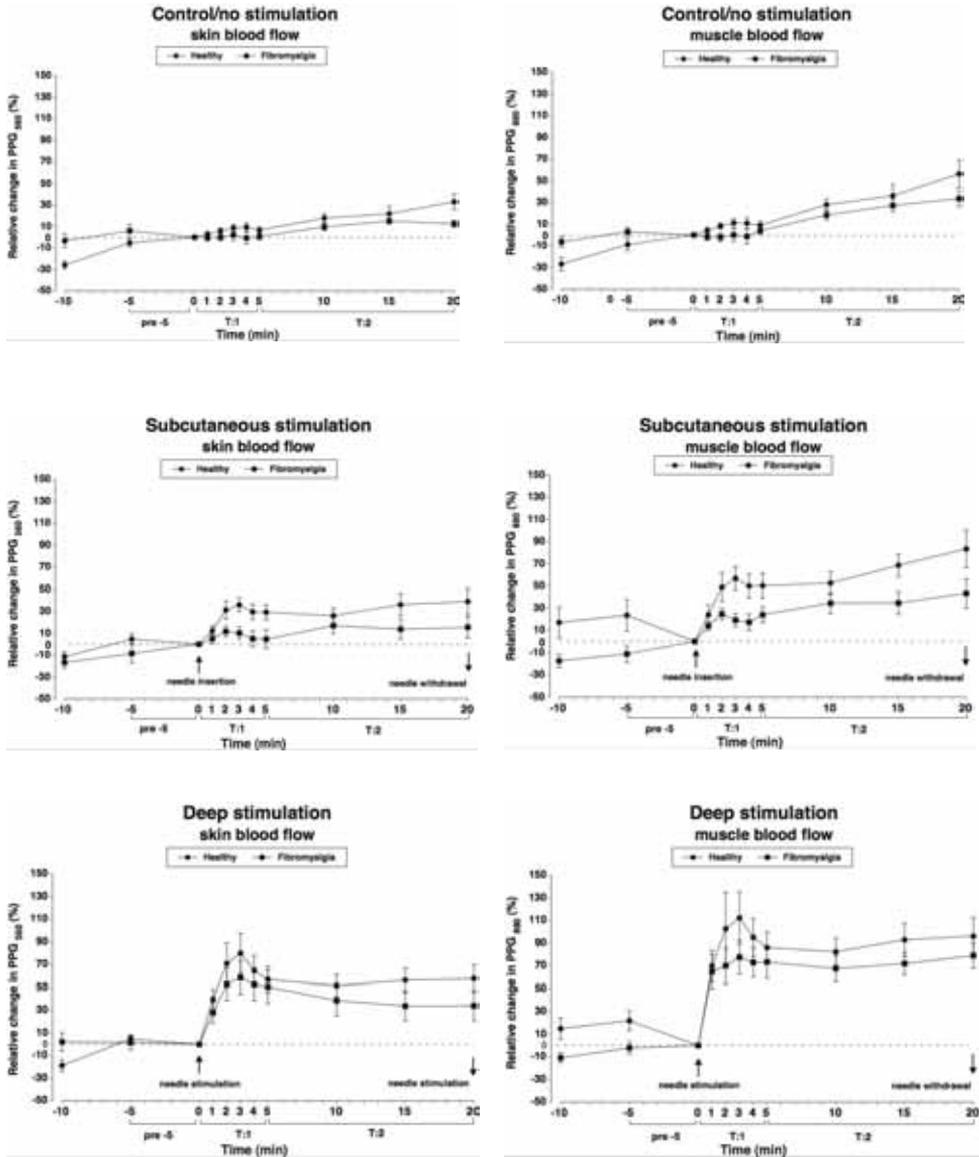


Figure 15: Relative changes (%) in skin and muscle blood flow with control (no stimulation) (a), subcutaneous needle insertion (SC) (b), and deep muscle stimulation (Deep) (c) in healthy subjects and fibromyalgia patients. The blood flow values are expressed as the mean (± 1 SEM) 60 s prior to intervention, and corresponding time point for control.

Table 3: VAS ratings of anxiety, pain and discomfort in healthy subjects (HS) (n=14) and fibromyalgia patients (FMS) (n=15) at deep (Deep) and subcutaneous (SC) modes of needle stimulation in the anterior tibial muscle and overlying skin

	HS			HS / FM ¹	FMS		
	mean	(SD)	range	p	mean	(SD)	range
Anxiety							
SC	2	(2.7)	0-8	ns	5	(14.2)	0-55
Deep	15	(18.7)	0-63	0.07	6	(12.2)	0-40
Between stimuli ² p	0.01				ns		
Pain							
SC	4	(9.4)	0-36	ns	6	(10.8)	0-35
Deep	26	(26.4)	0-75	ns	24	(23.5)	0-55
Between stimuli ² p	0.01				0.03		
Discomfort							
SC	1	(1.6)	0-5	0.08	0	(1.3)	0-5
Deep	21	(24.3)	0-73	0.04	7	10.0	0-30
Between stimuli ² p	0.01				0.03		

¹Mann Whitney-U test was used to test differences between groups. ²Wilcoxon signed-ranks test was used to test differences between SC and Deep.

The trapezius muscle

In Study VI, Deep consistently induced greater skin and muscle blood flow increases than SC in HS, whereas in FMS, SC induced either equal or even greater increases in blood flow than Deep. (**Figure 16, Table 4**) In addition, in FMS the effect on blood flow lasted longer after SC than after Deep.

The response to needle stimulation was generally less in TM, and only initially resulted in increased blood flow. No significant differences in blood flow changes existed between the groups with SC, whereas with Deep a consistent and significantly greater increase in muscle blood flow was induced in HS compared to both patient groups, as well as a trend toward a greater increase in skin blood flow. No significant differences existed between FMS and TM, although generally, the latter responded less.

At control no differences were found between left and right trapezius muscle blood flow change in any group. At SC a transient significant increase was found contralaterally in both HS and patients. A transient significant increase was also found contralaterally in HS at each of the three needle manipulations at Deep, whereas in FM patients contralateral muscle blood flow increased transiently only at the first manipulation. In TM patients no contralateral muscle blood flow increase was found at Deep. Generally, the contralateral increase in muscle blood flow was significantly less than in the stimulated muscle and apparent only at first min after the needle stimulation in the patients and during ~2 min in the HS.

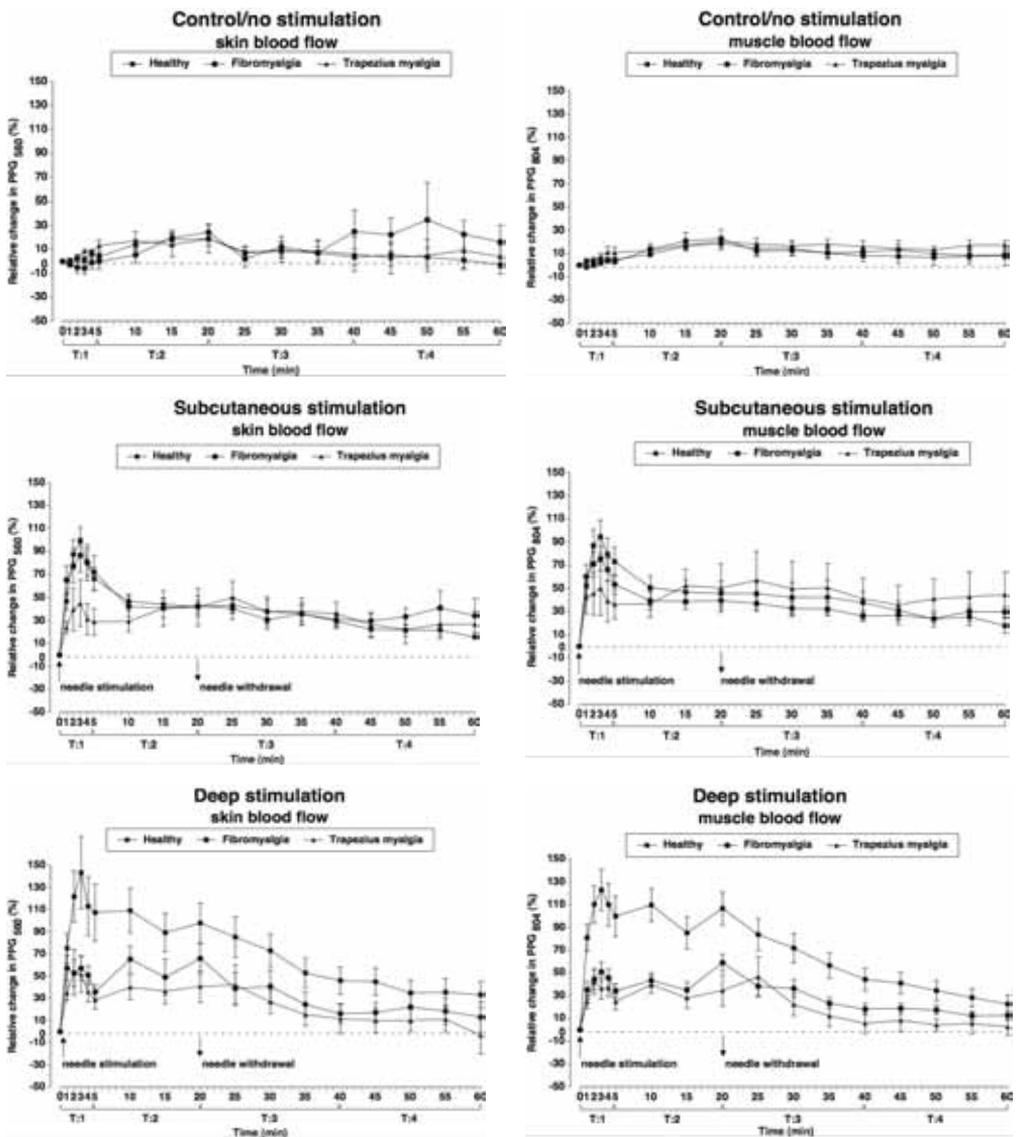


Figure 16: Relative changes (%) in skin and trapezius muscle blood flow with control (no stimulation), subcutaneous needle insertion (SC), and deep muscle stimulation (Deep) in healthy subjects, fibromyalgia patients and patients with trapezius myalgia. The blood flow values are expressed as the mean (± 1 SEM) 60 s prior to intervention, and corresponding time point for control

Table 4: Statistical results of relative skin blood flow (SBF) (a) and trapezius muscle blood flow (MBF) (b) changes between subcutaneous needle insertion (SC), deep muscle stimulation (Deep) and control at different time points in healthy subjects, fibromyalgia patients and patients with work-related trapezius myalgia

Time point	Healthy subjects (n = 19)		Fibromyalgia (n = 19)		Trapezius myalgia (n = 6)	
	p^1	Post hoc-test ²	p^1	Post hoc-test ²	p^1	Post hoc-test ²
(a) SBF						
T:1	< 0.01	Deep, SC > control Deep, SC > control;	< 0.01	Deep, SC > control; SC > Deep	0.03	Deep, SC > control
T:2	< 0.01	Deep > SC Deep, SC > control;	0.01	Deep, SC > control	ns	NA
T:3	0.01	Deep > SC	0.04	SC > control	ns	NA
T:4	ns	NA	ns	NA	ns	
(b) MBF						
T:1	< 0.01	Deep, SC > control Deep, SC > control;	< 0.01	Deep, SC > control; SC > Deep	0.01	Deep, SC > control
T:2	< 0.01	Deep > SC Deep, SC > control;	0.01	Deep, SC > control	ns	NA
T:3	0.01	Deep > SC	0.01	Deep, SC > control	ns	NA
T:4	0.06	NA	0.01	SC > control	ns	NA

T:1 denotes mean AUC for initial 5 min; T:2 denotes mean AUC for 5–20; T:3 denotes mean AUC for 20-40 min and T:4 denotes mean AUC for remaining 40-60 min averaged over 5 min post-stimulation periods. ¹Friedman’s test was used to test differences between control, SC and Deep within each group. ²Student-Newman-Keuls test was used for post hoc tests. N =not applicable; ns = not significant. > = significantly larger than

The multivariate analyses on all subjects and variables together revealed a significant intercorrelation between anthropometrics, spontaneous pain intensities, PPT (negatively) and AROM (negatively) variables. The three AUC variables 0-5 min, 5-20 min and 20-40 min of muscle blood flow with Deep showed significant correlations with this set of variables. The three AUC variables of muscle blood flow with Deep correlated positively and significantly with AROM, PPT and negatively (significantly) with all spontaneous pain intensity variables, symptom duration and age. They also correlated (positively) significantly with pain intensity experienced by the stimuli.

Comments

This study aimed at investigating blood flow response to needle stimulation at a spontaneously painful site in FMS and work-related, originally unilateral, TM patients, and at the corresponding site in HS. The stimuli were more intense in this study, in that three *DeQi* sensations were evoked, in contrast to only one in the previous studies. With SC, three needles were inserted within the area

permitted by the probe (\emptyset 7 mm), whereas only one needle was used in Studies IV and V. This approach was chosen in order to more resemble the ordinary clinical setting.

Unexpectedly, the TM patients presented with equal, or even worse, symptomatology than the FMS patients, including general pain. Neither duration nor intensity of symptoms differed between FMS and TM patients, whereas AROM was lower and age higher in the TM patients. Together with older age, the severe symptomatology might explain the lesser blood flow response in the trapezius muscle in these patients.

GENERAL DISCUSSION

Acupuncture

Evidence of effect in clinical conditions

The requirements set to obtain the status of a high quality randomised controlled study are not always fulfilled in clinical acupuncture trials. These include reasonably large trials, a range of assessment methods, adequate follow-up and double-blindness (Lewith and Vincent 1998). As with other physical treatment modalities double-blindness is not possible. For many conditions in which acupuncture is used the evidence is regarded as either insufficient or negative. This is to a large extent explained by methodological limitations of the trials and also by methodological principles followed by the reviewers.

Currently, evidence for an effect of acupuncture exists for the anti-emesis in nausea caused by pregnancy, surgery and chemotherapy (Vickers 1996) and acute dental pain (Ernst and Pittler 1998) and recently, a systematic review found existing evidence to support the value of acupuncture in the treatment of idiopathic headache (Melchart, Linde et al. 2001). The evidence from other systematic reviews of acupuncture is promising, such as the treatment of knee osteoarthritis (Ezzo, Hadhazy et al. 2001), but the evidence in most cases is considered insufficient to draw firm conclusions.

Reviews of acupuncture for the treatment of a heterogeneous range of common painful conditions are generally negative, including chronic pain (Ezzo, Berman et al. 2000; Lee 2000; NHS Centre for Reviews and Dissemination 2001) and results have been discordant for back pain (Ernst and White 1998; van Tulder, Cherkin et al. 1999; van Tulder, Cherkin et al. 2004). According to a recent editorial in *Pain*, the emerging results of current German mega-trials show that acupuncture reduces pain in ~ 44 % of patients, but not more so than a credible placebo procedure (Ernst 2004).

Criticism has been put forward that systematic reviews do not take into consideration the underlying pain mechanisms of the various conditions included, which is of crucial importance (Lundeberg, Hurtig et al. 1988; Thomas, Arner et al. 1992; Thomas and Lundeberg 1996; Carlsson and Sjölund 2001). It has been shown that pain conditions of neurogenic (Lewith, Field et al. 1983; Lundeberg, Hurtig et al. 1988) and idiopathic (Thomas, Arner et al. 1992) origin respond poorly or do not respond at all to acupuncture, and thus, should in systematic reviews not be mixed with nociceptive pain conditions, in which acupuncture is suggested to be beneficial (Lundeberg, Hurtig et al. 1988; Thomas, Arner et al. 1992; Thomas and Lundeberg 1996; Carlsson and Sjölund 2001).

In FMS, only one high quality study has been identified (Berman, Ezzo et al. 1999), showing positive short-term results on pain and other symptoms after EA (Deluze, Bosia et al. 1992). For asthma (McCarney, Brinkhaus et al. 2004) and tinnitus (Park, White et al. 2000) current review evidence is inconclusive and for smoking cessation (White, Resch et al. 1999) and weight loss (Ernst 1997) it is negative. A recent review on the use of alternative and complementary medicine for postmenopausal symptoms concluded, that at this time there is insufficient data to support the use of any alternative therapy in this condition (Kang, Ansbacher et al. 2002).

Acupuncture in fibromyalgia

A general hyperexcitability and a dysfunctioning pain inhibitory system may explain the common clinical finding of exaggerated pain response to sensory somatic stimulation such as acupuncture in FMS. In the study by Deluze (1992) adverse events, including unpleasantness of needle insertion and increase in symptoms in 16 % of the patients, were reported following EA treatment, as well as a dropout rate of 21 %. Otherwise beneficial short-term results were reported. Baldry (2002) suggested that only mild stimulation should be used in the treatment of myofascial trigger points and FMS to avoid worsening of pain.

FMS may not be a homogenous entity in terms of symptomatology and clinical characteristics, suggesting different aetiological and / or pathological mechanisms underlying symptoms (Henriksson and Sörensen 2002) (Sörensen, Bengtsson et al. 1997), and the existence of subgroups of FMS has been postulated (Hurtig, Raak et al. 2001). It has been suggested that acupuncture may be a rapid and effective treatment in both FMS and myofascial pain, but with clear differences in the duration of relief. In myofascial pain syndrome a long-lasting relief may be obtained, whereas in FMS only short-term responses occur (Baldry 1992). In a placebo-controlled acupuncture study on 50 patients with generalised tendomyopathy ("fibromyalgie-Syndrom") significant short term differences in general and regional pain and PPT were found in both active and placebo groups, although significantly better results were obtained in the acupuncture group (Lautenschläger, Schnorrenberger et al. 1989). In a written questionnaire 3 months after the last treatment, 56% of patients in the acupuncture group and 41% in the control group reported the treatment as successful, although no significant differences prevailed between groups. The pain alleviating effect was reported to last for 8 weeks in the acupuncture group and for 6 weeks in the control group. In both studies best pain alleviation was reported by those with neck pain in the acupuncture group, whereas no special region predominated in the control group (Lautenschläger, Schnorrenberger et al. 1989).

Since acupuncture is suggested to mainly exert pain relief in nociceptive pain conditions (Lundeberg, Hurtig et al. 1988; Carlsson and Sjölund 1994;

Thomas and Lundeberg 1996), these findings may be explained by different pain mechanisms within certain individuals as has been proposed. The improvement of pain and muscle tension within the neck-shoulder area could be a result of the locally applied needles improving muscle blood flow in an area involving nociceptive pain. The generalised pain, presumably caused by central plasticity (Clauw and Crofford 2003), was less affected by the treatment. It was further found that patients having initially relatively satisfactory sleep and well-being benefited most from acupuncture, whereas those in whom these variables were poor achieved only moderate and short-lived improvement. Although depression was not assessed, these findings appears to be in line with clinical observation that depressed patients generally tend to respond poorly to any physical treatment until the depression has been treated.

Acupuncture in postmenopausal women

EA was hypothesised to decrease vasomotor symptoms by increasing the production and release of central β -endorphin. However, the results of this study did not support this hypothesis, since both groups improved equally on psychological distress and experience of vasomotor symptoms and no difference between the groups was found.

Both superficial and deep acupuncture as well as EA have been shown to evoke activation in the somatosensory cortex, whereas only EA and Deep activated various limbic and subcortical structures. In the present study, the extremely superficially inserted needles evoked no or only minor sensation. It seems unlikely therefore that this mode of needling *per se* would evoke central effects such as increased β -endorphin activity. In contrast, it is plausible to assume pronounced non-specific effects. Psychological aspects will be discussed below.

Control procedures in the clinical studies

The control in Study I consisted of continuation of regular medication over 2-3 months. At the time this study was conducted, i.e. during late 80-ies, awareness and knowledge of non-specific effects, or placebo responses, in medical treatment was sparse. During the treatment period the patients had regular and frequent close contact with the therapist, whereas during the control period no such contact existed. Today, knowledge and significance of interactions between patient and therapist, regardless of treatment programme, is widespread. Thus, by employing the mode of control used in Study I, non-specific effects cannot truly be distinguished from effects caused by the needles.

In order to evaluate effects of treatment, a placebo control is needed in a randomised parallel-group design. Trials of acupuncture have to be single blind, with the patients not knowing which group they belong to. However, the choice of control group in acupuncture is far from simple. It has been argued that some

form of acupuncture placebo is preferable as control on the general principle that if true and placebo treatments are matched for all possible incidental factors, then differences between them can more confidently be attributed to specific effects of the acupuncture treatment (Vincent and Richardson 1986). The control manipulation should have a similar appearance to the study treatment but with small or no specific physiological effects, although maintaining its psychological impact (Vincent and Richardson 1986; Lewith and Vincent 1998; Ceccherelli, Gagliardi et al. 2000; White, Filshie et al. 2001). Although *minimal acupuncture* might have some physiological effect, it was denoted a true placebo, or *near-placebo*, control and recommended in clinical investigations on acupuncture effects (LeWITH and Vincent 1998).

The women in Study II were told that the aim of the study was to compare two modes of acupuncture, with or without electro-stimulation. A minimal acupuncture approach was used as placebo control manipulation. The somatic stimulation, however, was even less than that described in minimal acupuncture. This was achieved by inserting small-dimension needles extremely superficially, up to 15 cm away from the acupuncture points used in the EA group and with no further stimulation. This manoeuvre hardly elicited any sensation. Furthermore, some needles fell off immediately after attachment to the skin and some fell off during the treatment session. This approach was possible since all needles were out of sight for the women.

Over the last few years PET and fMRI imaging techniques have been used to elucidate acute central modulation following EA and Deep in human experimental pain models (Wu, Hsieh et al. 1999; Hui, Liu et al. 2000; Hsieh, Tu et al. 2001; Wu, Sheen et al. 2002). Both acupuncture and control manipulation, such as superficial tactile stimulation, superficial pricking or superficial needling (3-5 mm) increased activity in the somatosensory cortex. There was general agreement about modulation of activity in a network of limbic and subcortical structures (nucleus accumbens, amygdala, hippocampus, parahippocampus, hypothalamus, ventral tegmental area, anterior cingulate gyrus, caudate, putamen, temporal pole, and insula) in the human brain by both EA and Deep. In contrast, no modulation in these areas was shown in response to the various control manipulations or when the needle was left in tissue without further manipulation. In addition, very superficially inserted needles have previously been shown to neither elicit needle sensation nor discharge in cutaneous A β -, A δ - or C- fibres (Wang, Yao et al. 1985). These findings support the choice of placebo control in Study II and indicate that central modulation by the control manipulation *per se* was most probably not evoked.

Non-specific effects

Placebos are generally considered to be control treatments with similar appearance to the study treatment, but without their essential components. In the widely cited paper “The Powerful Placebo”, Beecher (1955) made an attempt to

combine the results of placebo effects from 15 randomised trials on different conditions. He reported considerable effects of placebo interventions, averaging around 30 %. The significance of this paper has, however, been questioned (Kienle and Kiene 1997; Hrobjartsson and Gotzsche 2003).

When comparing the effect of placebo with no treatment groups in a variety of clinical conditions, no statistical significant overall effect of placebo was found in studies with binary outcomes or in trials with continuous objective outcomes. However, a significant difference was observed between placebo and no-treatment groups in trials with continuous subjective outcomes and in trials involving the treatment of pain (Hrobjartsson and Gotzsche 2003). In contrast, to this conclusion, the postmenopausal women included in Study II, as well as another 21 women in a previous similarly designed study (Wyon 2002), improved in both subjective and objective variables. Both EA and the (near-) placebo groups in the two studies improved significantly regarding decrease in number of hot flushes, and changes in 24h urine excretion of CGRP in parallel with decrease in flushes were found in both groups in the previous study (Wyon 2002).

Explanations of non-specific effects

Various models have been used to explain non-specific effects, or placebo responses, e.g. anxiety, conditioning and expectancy theories. The anxiety theory states that placebo analgesia is due to reduction of anxiety (McGlashan, Evans et al. 1969). The conditioning theory assumes that the placebo effect is a conditioned response due to repeated associations between a conditioned stimulus (for instance the hospital, the therapist, pills, injections) and an unconditioned stimulus (the active ingredient of a treatment) (Wickramasekera 1980; Voudouris, Peck et al. 1985). The cognitive theory proposes that expectations and beliefs of analgesia play an essential role (Price, Milling et al. 1999).

The role of expectation has been extensively studied during the last years and have been proposed as the major determinant of placebo effects. The mechanisms leading to the release of endogenous opioids in placebo analgesia (Amanzio and Benedetti 1999; Benedetti, Arduino et al. 1999) and of endogenous dopamine in the placebo response of patients with Parkinson's disease (de la Fuente-Fernandez, Ruth et al. 2001) were believed to involve both conditioning and cognitive factors. In a recent study by Benedetti (2003), however, verbally induced instructions had no effect on hormonal secretion, whereas pain and motor performance were affected. The authors suggested that placebo responses are mediated by conditioning when unconscious physiological functions, such as hormonal secretion, are involved, whereas they are mediated by expectation in conscious physiological processes, such as pain and motor performance.

Not only the expectation of the subject but also the expectation, as well as the enthusiasm, interest and charisma of the therapist is important in producing non-specific effects (Turner et al., 1994; Wall, 1993; Richardsson, 1989).

Relaxation and stress reduction

According to the anxiety theory (McGlashan, Evans et al. 1969) non-specific effects of acupuncture might be expected to relate to stress and anxiety reduction. Such changes are most likely to occur in systems, which are at least partially under autonomic control (Richardsson 1989; Andersson and Lundeborg 1995). Given increased levels of sympathetic activity in postmenopausal women with vasomotor symptoms as well as in and patients with chronic pain, the regular rest and relaxation *per se* offered during repeated acupuncture sessions would be expected to decrease autonomic tone, and thus, indirectly contribute to the ameliorations of symptoms. Regular relaxation training has previously been shown to improve psychological well-being and to decrease climacteric symptoms (Wijma, Melin et al. 1997).

Context, social interaction and touch

The term *context effect* was recently introduced to stress the importance of the context in which a treatment is given (Di Blasi, Harkness et al. 2001). The importance of context was recently demonstrated by the use of hidden and open injections of analgesics in both clinical and experimental settings (Amanzio, Pollo et al. 2001). The authors found that hidden injections were significantly less effective than open injections, irrespective of true or placebo compounds. The authors also showed that the context effects were related to the endogenous system.

The needling procedure in the studies was not isolated from the context in which it was performed, implying a considerable amount of “hands-on” and friendly social interaction. All kinds of friendly social contact during which non-noxious and noxious sensory stimulation is given is suggested to induce a psycho-physiological response including calmness, sedation, relaxation, decreased sympathoadrenal activity and increased vagal nerve tone, as well as reduced reactivity to stressful or painful experiences, by the release of endogenous oxytocin (Uvnäs-Moberg, Bruzelius et al. 1993; Uvnäs-Moberg 1998; Lund, Yu et al. 2002). Oxytocin is suggested to be an important component of the mechanism mediating the health benefits and antistress effects of positive social interaction, characterised by physical contact. The anti-stress effect of oxytocin was also suggested more pronounced after repeated exposure. Furthermore, social interaction and activity also appear to be mediated, at least in part, by the opioid system (Olson, Olson et al. 1991).

Since many points were needled at each session the amount of tactile stimulation was considerable. An interesting, although speculative, aspect of touch in this context is the evidence of dual tactile innervation of the human

hairy skin. Touch stimulates activity in myelinated A β -fibres. However, highly sensitive tactile C-fibres (CT) are found in humans (Nordin 1990; Vallbo, Olausson et al. 1999). The functional properties of these afferents were suggested to differ from those of myelinated afferents. The CT-fibres were shown to respond particularly well to slow stroking of the skin. The functional role of these fibres in sensation is not clear. However, recently an association was shown between activation of CT- afferents in man and a faint sensation of pleasant touch (Olausson, Lamarre et al. 2002). Together with simultaneous fMRI findings, CT- afferents were suggested a system for limbic touch that might underlie emotional, hormonal and affiliate responses to caress-like, skin-to-skin contact between individuals.

Methodology - photoplethysmography

A non-invasive technique was evaluated for monitoring changes in pulsatile muscle blood perfusion in human utilizing PPG (Study III). The results indicate the potential of the method for monitoring local muscle blood perfusion, although some considerations still have to be accounted for.

The experiments clearly showed this method's ability to discriminate between blood perfusion at different depths when there is no change in the superficial blood perfusion. However, when there are also changes in the skin perfusion this will, to some extent, also influence measurement of deep blood perfusion. In the case of the tibialis anterior muscle this influence was shown to be of importance when the blood perfusion in the skin exceeded approximately 100 % of baseline value (Study III). The corresponding influence in the case of the trapezius muscle (Study VI) has been investigated in a pilot study and showed a limit of 120 % of baseline value. However, the optimal solution is of course to find a way to subtract the influence of superficial blood perfusion from the total flow signal in order to obtain the "true" blood perfusion in the muscle compartment underneath the probe. This involves empirical studies of the fractional influence of skin perfusion on muscle perfusion, as well as an automatic algorithm in combination with filtering modalities. These procedures are under way and will hopefully improve the technique.

One limitation of the technique was the heating effect of primarily the green light source, leading to a local temperature increase and effect on local blood perfusion. In the trapezius probe this influence was reduced by approximately 50 % by shortening the pulse length of the pulsed light (Study VI). Since changes in blood perfusion following needle stimulation were consistently compared to corresponding control values, this feature was assumed not to affect the results of the clinical experiments (Studies IV-VI) to a substantial degree.

Radiant power of the near-infrared light was shown to penetrate to a vascular depth of 13.0 mm from the skin surface in the case of the tibialis anterior muscle. During the assessment of the trapezius probe an optical fibre was

inserted into the trapezius muscle underneath the probe in 14 healthy subjects and connected to a POM for recording and confirmation that the light reached the muscle tissue. The results showed that the light penetrated down to a depth of 13.6 mm from the skin surface. Since the distance from skin to the fascia of the tibialis anterior muscle was in mean (SD) 5.4 (2.7) mm (Study III) and to the fascia of the trapezius muscle 5.8 (1.7) mm (Study VI), respectively, the near infrared light was assured to penetrate into muscle tissue enabling muscle blood flow recordings.

In these studies attention was directed to a pulsatile blood perfusion parameter when applying the custom-designed probe and PPG technique. However, from the PPG signal several other physiological parameters may be determined, such as heart and respiratory rate, and slow signal variations reflecting different features of the autoregulatory system.

Needle stimulation

Different patterns of blood flow responses in the tibialis anterior and trapezius muscles following needle stimulation were found between HS and FMS, and TM, patients. Whereas in HS the deep mode of stimulation was superior to SC independent of site of stimulation, blood flow increase in response to needling in FMS varied, depending on site of stimulation.

The patients experienced the subcutaneous insertion of the three small dimension needles in the trapezius muscle as painful as one deeply inserted needle, eliciting DeQi, whereas HS rated SC significantly less painful than Deep. A similar higher sensitivity to SC in FMS patients might have given rise to a significantly larger blood flow increase in the tibialis anterior muscle and overlying skin, although at this site the pain rating was at a similarly low level in both groups due to the low stimulation intensity. Although this site is mostly non-painful in FMS, it is embraced by a generalised hyperexcitability. These findings may be in accordance with experiments on neurogenic flare responses to noxious mechanical stimulation, showing exaggerated flares in FMS patients compared to healthy subjects (Gibson, Littlejohn et al. 1994).

HS and patients rated equal pain intensity in response to Deep stimulation in the tibialis and the trapezius muscle, respectively, yet muscle blood flow increase in the trapezius muscle was significantly less in FMS patients than HS. The reason for this difference is not known. However, the findings might indicate that in the spontaneously painful trapezius muscle of FMS, the mechanisms behind muscle blood flow increase in response to intramuscular noxious stimulation are different compared to the non-painful tibialis anterior muscle, as well as compared to the trapezius muscle of HS. The needle stimulation, and corresponding pain sensation, was distinctly less intense when stimulating the tibialis anterior muscle, which was exposed to one *DeQi*-stimulation, compared to needling the trapezius muscle which was accompanied

by three *DeQi*-stimuli. It could be that the lower level of noxious input to the tibialis anterior muscle might underlie the similar degree of blood flow increase in HS and FMS patients at this site. It should be noted, though, that the pain ratings of FMS patients at Deep could be underestimated, judging from the bodily reactions to the stimulation.

HS showed a tendency towards more anxiety before the needling and expressed more discomfort following the needling, compared to FMS patients. This was an unexpected finding since a common opinion is anxiousness and hypervigilance in FMS. In a recent study FMS patients appeared to be “psychophysically” identical to HS, except for a left-shift in their responsiveness to pressure and thermal stimuli (Petzke, Clauw et al. 2003). The authors suggested that expectancy to noxious stimuli or hypervigilance did not play a prominent role in their experiments.

An outline of the subcutaneous and deep modes of needle stimulation on skin and muscle blood flow in healthy subjects and patients with fibromyalgia is shown in **Table 4**.

Table 4: *An outline of the subcutaneous (SC) and deep (Deep) modes of needle stimulation on skin and muscle blood flow in healthy subjects and patients with fibromyalgia*

Site and stimulation	Healthy subjects		Fibromyalgia	
	Skin blood flow	Muscle blood flow	Skin blood flow	Muscle blood flow
The trapezius muscle				
SC	++	++	++++	++++
Deep	++++	++++	++	++
The tibialis muscle				
SC	0	0	+	++
Deep	++	+++	++	+++

Possible mechanisms

It has been suggested that blood flow increase in response to noxious stimulation is essentially mediated by antidromic release of vasodilator substances, such as CGRP, from free nerve endings in skin and muscle (Brain, Williams et al. 1985; Jänig and Lisney 1989; Kashiba and Ueda 1991; Holzer 1992; Porszasz and Szolcsanyi 1994; Brain and Cambridge 1996; Holzer 1998; Noguchi, Ohsawa et al. 1999; Sato, Sato et al. 2000; Loaiza, Yamaguchi et al. 2002). The mechanisms underlying the efferent actions of thin nerve fibres on local blood vessels are thought to be an axon reflex / axon response, as part of

neurogenic inflammation. However, interactions of the sympathetic nervous system cannot be ruled out.

Human nociceptive afferents are often vigorously activated by mechanical stimulation without eliciting painful sensations (Holzer 1992; Koltzenburg and Handwerker 1994). Thus, an axon reflex vasodilatation could be elicited by activation of nociceptors even in the absence of a conscious pain perception (Koltzenburg and Handwerker 1994; Magerl and Treede 1996). This may explain the blood flow increase in the tibialis muscle in eight of fourteen HS receiving non-painful SC. When a mechanical stimulation exceeded the pain threshold, however, the vasodilatation responses were increased both in magnitude and duration (Koltzenburg and Handwerker 1994).

Normally, antidromic stimulation of A β -fibres does not evoke vasodilatation (Jänig and Lisney 1989). However, in areas of allodynia A β -beta fibre-evoked skin vasodilatation has been found and was suggested to result from antidromic activation of nociceptive cutaneous afferent fibres by dorsal root reflexes (Cervero and Laird 1996; Gottrup, Andersen et al. 2000; Garcia-Nicas, Laird et al. 2001). It is not known whether A β -fiber activation was of importance in blood flow increase in the patients in the present studies, although activity in these fibres has previously been found during acupuncture (Wang, Yao et al. 1985).

Different patterns of blood flow response

Mechano-insensitive C-nociceptors

A substantial amount of nociceptors are mechanically insensitive afferents, having very high mechanical thresholds or are unresponsive to mechanical stimuli in normal skin (Schmidt, Schmelz et al. 1995; Torebjörk 1999). In hyperalgesic skin induced by inflammatory mediators, however, these receptors are shown to respond readily to local pressure (Torebjörk 1999), although not automatically increasing pain sensation (LaMotte, Shain et al. 1991). It was recently suggested that mechano-insensitive, and not polymodal C-fibres, mediate the axon reflex flare in human skin, although some of the polymodal C-fibres might induce a brief increase in blood flow (Schmelz, Michael et al. 2000). The activation of mechano-insensitive C-fibres was assumed to explain the findings of flares that were considerably larger than the receptive fields of polymodal C-nociceptors (Schmelz, Michael et al. 2000). In accordance with these findings significantly larger mechanically induced neurogenic flare responses in FMS, compared to HS, have been reported (Gibson, Littlejohn et al. 1994). It may be that differences in blood flow increase between HS and FMS patients in response to SC in the present studies may reflect involvement of an altered activity in mechano-insensitive C-nociceptors.

Warmth sensation

HS and FMS patients in Study VI were asked to indicate the extent of warmth sensation on a body chart following the needling. Large inter-individual variations were found, ranging from no sensation of warmth, a spot around the needle or upper part of the shoulder, to covering the ipsilateral shoulder, neck, cheek, arm and two thirds of the back. Drawings of warmth sensation of one HS with the SC and Deep stimuli are shown in **Figure 17**.

A few patients indicated an initial cooling sensation, indicating an interaction with sympathetic vasoconstrictor activity (Ochoa, Yarnitsky et al. 1993; Sugiyama, Xue et al. 1995; Häbler, Wasner et al. 1997). Normally, antidromic vasodilatation is suggested to override sympathetic vasoconstriction, however, at high levels of sympathetic activity, sympathetic vasoconstriction can suppress antidromic vasodilatation (Häbler, Wasner et al. 1997).

One or two subjects exposed bilateral extension of warmth sensation, extending to the upper part of the neck-shoulder region. Bilateral and large ipsilateral areas of warmth sensation might indicate involvement of dorsal root reflexes (Sluka, Willis et al. 1995; Willis 1999; Lin, Zou et al. 2000) or dichotomising nerve fibres (Dawson, Schmid et al. 1992).

Autonomic nervous system

Chronic pain may lead to plastic changes in the sympathetic nervous system (Roatta, Kalezic et al. 2003) and it has been suggested that patients with FMS display a prominent dysautonomia (Martinez-Lavin 2002). Both NA and NPY are released from sympathetic nerves and the adrenal medulla during stress and exercise. While NA plays a major role during conditions of acute intense stress, release of NPY is characterised by slow onset and long duration, i.e. during prolonged stress (Zukowska and Lee 2003). Both substances are suggested to inhibit the efferent function of free nerve endings in the periphery, which leads to vasoconstriction (Maggi 1991; Holzer 1992; Ochoa, Yarnitsky et al. 1993; Häbler, Wasner et al. 1997; Zukowska and Lee 2003). NPY levels in plasma was suggested to increase, especially when combined with hypoxia (Maggi 1991; Zukowska and Lee 2003). Higher levels of NPY in plasma have been found in FMS patients compared to healthy controls (Anderberg, Liu et al. 1999).

Physiological function of the vascular system in the long term depends on a balanced interaction between all vascular control systems (Holzer 1992).

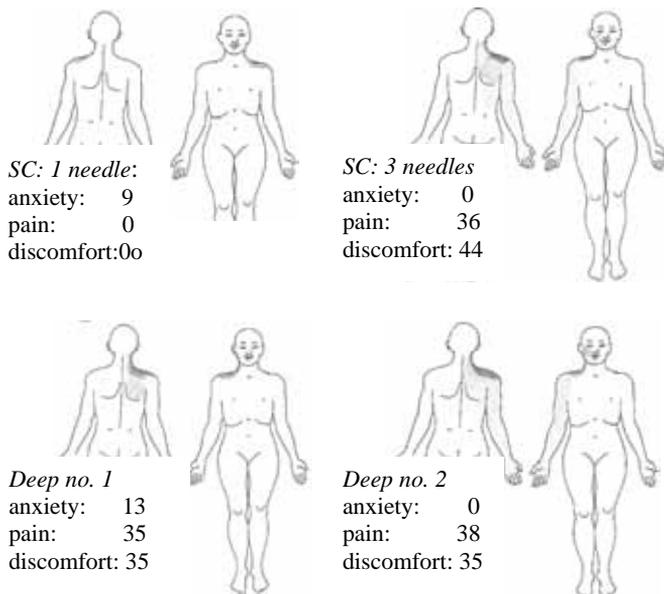


Figure 17: Warmth sensations experienced by one healthy subject at different occasions with subcutaneous needle stimulation using one or three small dimension needles (SC) and with deep muscle stimulation (Deep). VAS ratings of anxiety, pain and discomfort are shown with the stimuli are shown.

Imbalance in these interactions, e.g. between vasodilator and sympathetic vasoconstrictor neurones, is liable to cause pathological changes in the vascular system and in mechanisms depending on the vascular system. Sympathetic nerve activity, or administration of NA, was shown to counteract the afferent nerve-mediated changes in skin microcirculation (Holzer 1998). With this background it may be speculated whether release of vasoactive substances in the trapezius muscle in response to deep muscle stimulation was suppressed by increased sympathetic tone in the patients as opposed to HS.

The initial short-lasting increase that was shown in contralateral trapezius muscle blood flow immediately with the stimuli may represent a sympathetic stress response. This would be in line with previously detected short-lasting increases in sympathetic nerve activity at each needle stimulation in healthy subjects (Sugiyama, Xue et al. 1995). Interestingly, this response also differed between HS and patients, indicating involvement of sympathetic nerves in the in the abnormal blood flow response to needle stimulation in the trapezius muscle of the patients. However, no differences were found between HS and FMS patients in the tibialis muscle blood flow on contralateral side.

Multivariate analyses

Somatosensory disturbances are well established phenomena in FMS (Kosek, Ekholm et al. 1996; Mense 2000) and may be present in chronic TM, as well (Leffler, Hansson et al. 2002; Leffler, Hansson et al. 2003). Due to the limited number and severely affected patients with TM in Study VI, the results of needle stimulation in this group are preliminary and should be cautiously interpreted. However, signs of hypesensitivity in the TM patients in this study, adding to the

original symptoms, might indicate less blood flow increase in response to needle stimulation in these patients. The present findings of different patterns of blood flow response following needle stimulation between HS and patients might be the result of altered somatosensory processing in the patients.

Taking all subjects and variables together, blood flow change in the trapezius muscle with Deep was negatively correlated with symptom intensity and age and positively correlated with AROM and PPT, and also positively correlated to the pain evoked by the stimulation. Thus, variables obtained both prior to the stimulation and during the stimulation, were significantly related to blood flow change in the trapezius muscle. The significance of age was also apparent in Studies IV and V in that larger blood flow increases were generally found in younger subjects.

Clinical perspectives

The findings of different patterns of blood flow response to needle stimulation in FMS / TM patients compared to HS, presumably reflecting an abnormal somatosensory pain processing, may in the future be an aid in diagnostics and research on muscle pain conditions.

Vascular nutrient and hormone delivery to skeletal muscle plays a major role in the regulation of metabolism in skeletal muscle (Clark, Newman et al. 1998). Inactivity and stress each contribute to poor nutritive flow in muscle and the only known mechanisms for gaining full nutritive flow is to overcome the vasoconstrictor activity closing the capillaries, i.e. reduce catecholamine levels, or exercise muscle causing the release of endogenous vasodilators (Clark, Newman et al. 1998). CGRP-related vasodilatation in skeletal muscle may have physiological relevance to the supply of sufficient blood flow to muscles during muscle exercise (Mense and Meyer 1985; Sato, Sato et al. 2000) and CGRP is suggested important for explaining the effect of acupuncture on muscle pain relief (Sato, Sato et al. 2000).

Ischaemic rest pain and intermittent claudication in the leg are effectively treated with sympathetic blockade. In FMS patients a total block of sympathetic activity by a stellate ganglion blockade was shown to result in a markedly reduction of rest pain and number of tender points and increase in skin temperature (Bengtsson and Bengtsson 1988). This indicates that the increased blood flow may have been involved in the reduction of pain, and might support the findings of significant pain relief in the neck-shoulder region after acupuncture in these patients, assuming an increased muscle blood flow was induced (Study I). Thus, acupuncture therapy may have a place in the treatment of nociceptive muscle pain, because of its potential to improve blood flow in muscle. The existence of hyperexcitability, however, should be taken into account when dosing the intensity of stimulation, and gentle and / or superficial stimulation may be the most appropriate. It is important to

stress, however, that effects of acupuncture on generalised symptoms in FMS seem weak.

Finally, non-specific effects, such as those caused by relaxation and anxiety reduction, related to therapy should be utilized to reduce sympathetic activity and catecholamine levels in order to further decrease sympathetic vasoconstrictor activity.

The involvement of endogenous opioids in the mechanisms of both non-specific and specific effects of acupuncture may in part explain the obvious difficulties in obtaining evidence for the efficacy of acupuncture in various trials.

CONCLUSIONS

1. Acupuncture may be used as an adjunct for the alleviation of neck-shoulder symptoms in certain FMS patients, but it is not an alternative as the sole treatment. The effect on generalised symptoms was of short duration and appeared only in patients with relative good well-being and sleep.
2. Electro-acupuncture significantly decreased psychological distress and experience of climacteric symptoms in postmenopausal women but no more than a near-placebo control, implying pronounced non-specific effects.
3. Photoplethysmography (PPG) has the potential to non-invasively monitor changes in muscle blood flow, although further development is necessary.
4. Needle stimulation induces increased muscle blood flow in healthy subjects in the tibialis anterior and trapezius muscles alike, with deep muscle stimulation combined with eliciting the *DeQi*-sensation causing the greatest increases.
5. FMS patients, and probably patients with severe work-related chronic trapezius myalgia, show different patterns of blood flow response following needle stimulation, which might reflect an abnormal nervous processing of somatosensory impulses.
6. The existence of hyperexcitability should be taken into consideration when dosing the intensity of acupuncture in patients with chronic muscle pain.

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to all of those colleges, friends and family who supported me in various ways. Without their help and encouragement over the years this thesis would not have been possible.

In particular, I wish to express my gratitude to:

All patients, who took part of the studies, for spending a lot of time and effort, without whom there would have been no results to report.

All healthy subjects kindly taking their time and enduring some pain to participate in these studies.

My main tutor Professor Björn Gerdle, who saw me, believed in me and provided me facilities to finish this thesis. Perhaps his belief in me was too big, since he was not always there when I wanted, but when he was, his professional support, active interest and constructive criticisms gave me new courage and energy.

My co-tutor, collaborator and co-author Lars-Göran Lindberg, associate professor at the Department of Biomedical Engineering, who with patience and a big heart introduced me in the field of high-technology, with which I was not too familiar, and for generously sharing his knowledge in photoplethysmography. Although he was “lost” at times I knew he would turn up for new tests, fruitful discussions and with great enthusiasm bringing plans for the future.

Med. Dr. Jan Sörensen, head of the Pain and Rehabilitation Center, who generously provided me facilities, which made it possible to concentrate on my research.

My co-authors Med. Dr. Qiuxia Zhang, associate professor Jorma Styf, Med. Dr Britt Larsson, associate professor Klaas Wijma, Med Dr. Yvonne Wyon, and professor Mats Hammar.

Professor Sven Andersson and professor Thomas Lundeberg, who introduced me in the field of pain physiology and science of acupuncture near 20 years ago and ever since generously gave their support and constructive criticism.

Associate professor KG Henriksson, for his always-encouraging attitude, comments on manuscripts and generous sharing his great knowledge in muscle pain.

Associate professor Eva Haker, Med.Dr. Gunilla Brodda-Jansen and associate professor Ann Bengtsson for their constructive criticism, fruitful discussions and advices, although I did not follow them all.

Per Sveider, the Department of Biomedical Engineering, for his skilful technical assistance.

Martin Eneling, who helped me with huge amounts of data and signal analyses in the last study and never let me feel stupid in my technical shortcomings.

Ann-Katrin Persson, who helped me with the initial manual signal analyses.

Per Lagman and Kjell Thörnlund at MediaCenter for their professional assistance with graphs, pictures and posters and for their great patience until I was satisfied.

My friends and colleges at the Department of Rehabilitation Medicine: Michael Peolsson, for Ultrasound measurements and for his never-ending patience in helping me with tricky computers, Torbjörn Falkner, who came just in time to assist in my final writings, Barbro Larsson and Kersti Samuelsson for their encouraging and positive attitudes, knowing exactly what life looks like just now, and Lena Lindgren for secretarial assistance and everyday support, being it sweet cookies, when I needed them most.

My colleges at the Pain and Rehabilitation Center for their interest, support and participation in various studies.

Finally, I wish to thank my family for patience and support during the years.

The studies in this thesis have been supported by by grants from the County Council in Östergötland, The Swedish Rheumatism Association, the Foundation for Acupuncture and Alternative Biological Treatment Methods, and The division of Pain and Sensory Stimulation for Physiotherapists in Sweden.

SAMMANFATTNING PÅ SVENSKA

Akupunktur ingår som en del i traditionell kinesisk medicin (TCM) och har använts i över 2000 år för att lindra sjukdom och symptom. I Sverige blev akupunktur godkänd som smärtlindringsmetod inom Hälso- och Sjukvården 1984. Sedan nästan 10 år är akupunktur jämställd med övrig behandling i sjukvården vilket innebär, att akupunktur kan användas även för behandling av annat än smärta. Förutsättningen är emellertid, att det finns tillräckligt med vetenskapliga belägg, s.k. evidens, för detta. I de allra flesta fall saknas det idag. För att säkerställa att evidens föreligger krävs omfattande forskning om effekter av akupunktur.

Syftet med de olika studierna i avhandlingen var att belysa och studera psykologiska och fysiologiska aspekter och effekter av akupunktur och nålstimulering. Effekt på blodflöde i hud och muskel undersöktes på friska personer och på patienter med kronisk muskelsmärta. Normalt krävs ett mindre kirurgiskt ingrepp för att mäta blodflöde i muskel, men i dessa studier användes en mätmetod, som enkelt och utan ingrepp (icke-invasivt) i normala fall används för att mäta blodflöde i huden, s.k. fotopletysmografi (PPG, eng.). Med hjälp av ny teknik användes PPG i dessa studier för att mäta även muskelblodflöde. En studie för utvärdering av den nya PPG-tekniken ingick också i avhandlingen.

Utvärderingen av mätmetoden visade goda möjligheter att mäta muskelblodflöde icke-invasivt med hjälp av PPG. Hos friska personer blev effekten på blodflödet störst vid djup stimulering i muskeln och där den s.k. *DeQi*-känslan framkallades (som vid klassisk akupunktur). Hos patienter med fibromyalgi var nålstimulering i huden lika, eller t.o.m. mer, effektiv att öka muskelblodflödet i skuldran än den djupa nålstimuleringen. De olika mönstren av blodflödesökning mellan de friska personerna och patienterna kan bero på ett förändrat reaktionssätt i nervsystemet som svar på smärtsam stimulering.

I två kliniska studier studerades den smärtlindrande effekten av manuell akupunktur vid fibromyalgi och effekten av elektroakupunktur på stress och klimakteriebesvär hos kvinnor i övergångsåldern. Akupunktur vid fibromyalgi visade sig ha bäst smärtlindrande effekt i nack-skulderområdet, medan effekten på de generella symptomen var kortvarig. Patienter som mådde och sov relativt bra erhöll bäst effekt. Efter en behandlingsserie, bestående av elektroakupunktur, minskade stress och klimakteriebesvär påtagligt hos kvinnorna i övergångsåldern, men inte mer än hos en grupp kvinnor, som fick en kontrollbehandling bestående av mycket ytligt placerade nålar i huden. Detta tyder på att en betydlig del av behandlingsresultatet utgjordes av ospecifika effekter eller, s.k. eller placeboeffekter.

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